



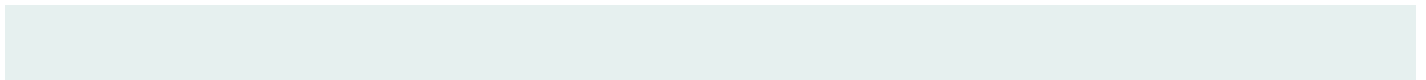
Public Health Division  
Environmental Public Health Section

**2026**

# Appendices to the Toxicity Reference Value Support Document

**Rules Advisory Committee Version**

**January 12<sup>th</sup>, 2026**



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## **Appendix A: OHA's Response to ATSAC Feedback**

# Appendix A: OHA's Response to ATSAC Feedback

## Section 1 Purpose

Overall, ATSAC members supported the approach that OHA used to adopt and generate the TRV proposals (see Appendices B-J). This appendix summarizes:

- ATSAC's feedback to OHA during and after ATSAC meetings on the TRV proposals (ATSAC meetings #4-7) where ATSAC members requested changes to OHA's processes, specific TRV proposals, and materials, and
- OHA's responses to this ATSAC feedback.

To compile this document, OHA staff reviewed all the ATSAC meeting minutes from the meetings related to the TRV proposals (meetings #4-7, Appendices D and E) and all the ATSAC written responses related to TRV proposals (Appendix H). For more details on ATSAC's comments, refer to the original ATSAC meeting minutes and written comments in subsequent appendices. Some ATSAC comments in this document reflect general themes from more than one ATSAC member and other ATSAC comments are specific comments from one ATSAC member.

ATSAC comments are organized by the workbook or specific ATSAC document (the specific ATSAC documents have since become chapters in the TRV Support Document). The numbers next to the ATSAC comments in this document do not reflect the comment's importance, rather are just an organizational tool for reader's reference.

There were some TRV proposals that OHA discussed with ATSAC either in email threads outside of meetings or in special meetings focused on specific TACs (such as ATSAC meeting #3 on manganese and ATSAC meeting #8 on diesel particulate matter). Refer to Section 7 of this Appendix for a summary of where to find ATSAC feedback and OHA responses on specific toxic air contaminants not covered in ATSAC meetings #4-7. ATSAC feedback on the overall TRV review and update process was captured during ATSAC meeting #2 and ATSAC feedback from that meeting can be found in Appendix B and OHA responses can be found in Appendix J.

## Section 2 TRVs that changed after the ATSAC

After the ATSAC meetings, OHA updated **113 TRVs** across **70 toxic air contaminants** in preparation for the Rules Advisory Committee (RAC) meetings. Of these 113 TRVs,

- 92% (104) were changes in direct response to ATSAC feedback
- 5% (6) were a result of an authoritative source update
- 3% (3) were an error correction that OHA staff identified after the ATSAC meetings.



OHA **changed** 111 proposed TRVs and **added** 2 new proposed TRVs in the TRV Workbooks after the ATSAC meetings. Of note, some ATSAC feedback applied to methods or approaches that applied to many TACs or groups of TACs. ATSAC member's feedback on *chlorinated and brominated dioxins and furans & dioxin-like polychlorinated and polybrominated biphenyls* (see detailed explanations in Chapter 3 and Appendix R) led to OHA updating 92 TRV proposals, counting both cancer and noncancer TRVs for each congener.

Overall, the 113 TRV changes after the ATSAC meetings are summarized in Table A-1. To prepare TRVs and related materials for the series of RAC meetings, OHA checked for and incorporated new updates to inhalation TRVs from all authoritative sources as of **July 21, 2025**. To learn more about key dates relevant to updating TRVs during each stage of this Rulemaking, refer to Chapters 2 and 4 in the TRV Support Document.

**Table A-1.** Additional information on the **113** proposed TRVs across **70** toxic air contaminants that OHA staff updated after ATSAC's review and before the RAC meetings.

| CAS RN   | Name of the Toxic Air Contaminant or Group | Number of TRVs in Group | Inhalation TRV Category | TRV Proposed to ATSAC as of 1/15/2025 (µg/m <sup>3</sup> ) | TRV Proposed to RAC as of 7/21/2025 (µg/m <sup>3</sup> ) | Reason for Change after ATSAC Meetings | Where to Learn More about Change                                                                                    |
|----------|--------------------------------------------|-------------------------|-------------------------|------------------------------------------------------------|----------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 67-64-1  | Acetone                                    | 1                       | Noncancer Chronic       | 11,000                                                     | 3,200                                                    | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> </ul>                                          |
| 107-02-8 | Acrolein                                   | 1                       | Acute                   | 7                                                          | 2.5                                                      | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> <li>TRV Support Document, Chapter 4</li> </ul> |
| 71-43-2  | Benzene                                    | 1                       | Acute                   | 29                                                         | 30                                                       | Authoritative Source Update            | <ul style="list-style-type: none"> <li>TRV Support Document, Chapter 4</li> </ul>                                   |
| 71-43-2  | Benzene                                    | 1                       | Noncancer chronic       | 3                                                          | 6                                                        | Authoritative Source Update            | <ul style="list-style-type: none"> <li>TRV Support Document, Chapter 4</li> </ul>                                   |

| CAS RN     | Name of the Toxic Air Contaminant or Group | Number of TRVs in Group | Inhalation TRV Category | TRV Proposed to ATSAC as of 1/15/2025 (µg/m <sup>3</sup> ) | TRV Proposed to RAC as of 7/21/2025 (µg/m <sup>3</sup> ) | Reason for Change after ATSAC Meetings | Where to Learn More about Change                                                                                    |
|------------|--------------------------------------------|-------------------------|-------------------------|------------------------------------------------------------|----------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| 10294-34-5 | Boron trichloride                          | 1                       | Acute                   | 2,200                                                      | 94                                                       | Error correction                       | <ul style="list-style-type: none"> <li>This appendix, see below</li> </ul>                                          |
| 74-83-9    | Bromomethane {methyl bromide}              | 1                       | Acute                   | 350                                                        | 190                                                      | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> <li>TRV Support Document, Chapter 5</li> </ul> |
| 106-94-5   | 1-Bromopropane {n-propyl bromide}          | 1                       | Noncancer chronic       | 100                                                        | 1.7                                                      | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> </ul>                                          |
| 78-93-3    | 2-Butanone {methyl ethyl ketone (MEK)}     | 1                       | Noncancer Chronic       | 5,000                                                      | No proposed value                                        | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> </ul>                                          |
| 75-15-0    | Carbon disulfide                           | 1                       | Acute                   | 6,200                                                      | 600                                                      | Authoritative Source Update            | <ul style="list-style-type: none"> <li>TRV Support Document, Chapter 4</li> </ul>                                   |
| 75-15-0    | Carbon disulfide                           | 1                       | Noncancer Chronic       | 110                                                        | 300                                                      | Authoritative Source Update            | <ul style="list-style-type: none"> <li>TRV Support Document, Chapter 4</li> </ul>                                   |
| 4170-30-3  | Crotonaldehyde                             | 1                       | Noncancer Chronic       | 1.1                                                        | 2.7                                                      | Error correction                       | <ul style="list-style-type: none"> <li>This appendix, see below</li> </ul>                                          |
| 106-46-7   | 1,4-dichlorobenzene {p-Dichlorobenzene}    | 1                       | Acute                   | 12,000                                                     | 8,700                                                    | Authoritative Source Update            | <ul style="list-style-type: none"> <li>TRV Support Document, Chapter 4</li> </ul>                                   |
| 106-46-7   | 1,4-dichlorobenzene                        | 1                       | Noncancer Chronic       | 60                                                         | 5                                                        | Authoritative Source Update            | <ul style="list-style-type: none"> <li>TRV Support Document, Chapter 4</li> </ul>                                   |

| CAS RN   | Name of the Toxic Air Contaminant or Group | Number of TRVs in Group | Inhalation TRV Category | TRV Proposed to ATSAC as of 1/15/2025 ( $\mu\text{g}/\text{m}^3$ ) | TRV Proposed to RAC as of 7/21/2025 ( $\mu\text{g}/\text{m}^3$ ) | Reason for Change after ATSAC Meetings | Where to Learn More about Change                                                                                                        |
|----------|--------------------------------------------|-------------------------|-------------------------|--------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
|          | {p-Dichlorobenzene}                        |                         |                         |                                                                    |                                                                  |                                        |                                                                                                                                         |
| 302-01-2 | Hydrazine                                  | 1                       | Acute                   | 29                                                                 | 5.2                                                              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> <li>TRV Support Document, Chapter 5</li> </ul>                     |
| 67-56-1  | Methanol                                   | 1                       | Noncancer Chronic       | 20,000                                                             | 4,000                                                            | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> </ul>                                                              |
| Various  | PBB Group                                  | 12                      | Cancer                  | Range: $2.6 \times 10^{-7}$ to $9.1 \times 10^{-4}$                | Range: $5.3 \times 10^{-7}$ to $8.8 \times 10^{-4}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> <li>Appendix S</li> <li>TRV Support Document, Chapter 3</li> </ul> |
| Various  | PBB Group                                  | 4                       | Noncancer Chronic       | Range: $4.0 \times 10^{-4}$ to $4.0 \times 10^{-1}$                | Range: $8.0 \times 10^{-4}$ to $1.3 \times 10^{-1}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> <li>Appendix S</li> <li>TRV Support Document, Chapter 3</li> </ul> |
| Various  | PBDD & PBDF Group                          | 15                      | Cancer                  | Range: $2.6 \times 10^{-8}$ to $9.1 \times 10^{-5}$                | Range: $6.6 \times 10^{-8}$ to $2.6 \times 10^{-5}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>This appendix, see below</li> <li>Appendix S</li> <li>TRV Support Document, Chapter 3</li> </ul> |

| CAS RN         | Name of the Toxic Air Contaminant or Group | Number of TRVs in Group | Inhalation TRV Category | TRV Proposed to ATSAC as of 1/15/2025 ( $\mu\text{g}/\text{m}^3$ ) | TRV Proposed to RAC as of 7/21/2025 ( $\mu\text{g}/\text{m}^3$ ) | Reason for Change after ATSAC Meetings | Where to Learn More about Change                                                                                                              |
|----------------|--------------------------------------------|-------------------------|-------------------------|--------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Various</i> | PBDD & PBDF Group                          | 15                      | Noncancer Chronic       | Range: $4.0 \times 10^{-5}$ to $1.3 \times 10^{-1}$                | Range: $1.0 \times 10^{-4}$ to $4.0 \times 10^{-2}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> <li>• Appendix S</li> <li>• TRV Support Document, Chapter 3</li> </ul> |
| <i>Various</i> | PCB Group                                  | 12                      | Cancer                  | Range: $2.6 \times 10^{-7}$ to $9.1 \times 10^{-4}$                | Range: $5.3 \times 10^{-7}$ to $8.8 \times 10^{-4}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> <li>• Appendix S</li> <li>• TRV Support Document, Chapter 3</li> </ul> |
| <i>Various</i> | PCB Group                                  | 4                       | Noncancer Chronic       | Range: $4.0 \times 10^{-4}$ to $4.0 \times 10^{-1}$                | Range: $8.0 \times 10^{-4}$ to $1.3 \times 10^{-1}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> <li>• Appendix S</li> <li>• TRV Support Document, Chapter 3</li> </ul> |
| <i>Various</i> | PCDD & PCDF Group                          | 15                      | Cancer                  | Range: $2.6 \times 10^{-8}$ to $9.1 \times 10^{-5}$                | Range: $6.6 \times 10^{-8}$ to $2.6 \times 10^{-5}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> <li>• Appendix S</li> <li>• TRV Support Document, Chapter 3</li> </ul> |

| CAS RN         | Name of the Toxic Air Contaminant or Group | Number of TRVs in Group | Inhalation TRV Category | TRV Proposed to ATSAC as of 1/15/2025 ( $\mu\text{g}/\text{m}^3$ ) | TRV Proposed to RAC as of 7/21/2025 ( $\mu\text{g}/\text{m}^3$ ) | Reason for Change after ATSAC Meetings | Where to Learn More about Change                                                                                                              |
|----------------|--------------------------------------------|-------------------------|-------------------------|--------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Various</i> | PCDD & PCDF Group                          | 15                      | Noncancer Chronic       | Range: $4.0 \times 10^{-5}$ to $1.3 \times 10^{-1}$                | Range: $1.0 \times 10^{-4}$ to $4.0 \times 10^{-2}$              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> <li>• Appendix S</li> <li>• TRV Support Document, Chapter 3</li> </ul> |
| 335-76-2       | Perfluorodecanoic acid (PFDA)              | 1                       | Noncancer Chronic       | 0.053                                                              | 0.000007                                                         | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• Appendix R</li> <li>• TRV Support Document, Chapter 5</li> </ul>                                     |
| 103-65-1       | n-Propylbenzene                            | 1                       | Cancer                  | 0.4                                                                | No value                                                         | Error correction                       | <ul style="list-style-type: none"> <li>• This appendix below</li> </ul>                                                                       |
| 75-56-9        | Propylene oxide                            | 1                       | Acute                   | 460                                                                | 260                                                              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> <li>• TRV Support Document, Chapter 5</li> </ul>                       |
| 2699-79-8      | Sulfuryl fluoride {Vikane}                 | 1                       | Noncancer Chronic       | --                                                                 | 50                                                               | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> </ul>                                                                  |
| 2699-79-8      | Sulfuryl fluoride {Vikane}                 | 1                       | Acute                   | --                                                                 | 3,100                                                            | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> </ul>                                                                  |
| 108-88-3       | Toluene                                    | 1                       | Noncancer Chronic       | 3,800                                                              | 420                                                              | ATSAC Feedback                         | <ul style="list-style-type: none"> <li>• This appendix, see below</li> </ul>                                                                  |

OHA staff made other types of changes to information in the TRV Workbooks in response to ATSAC feedback that did not change the actual TRVs, such as

- the names of a few column headers,
- the order that columns appeared,
- added clarity about whether authoritative sources had applied a dosimetric adjustment factor in their derivation, and
- notes about whether multi-pathway adjustment factors or early life adjustment factors need to be applied to a given TRV when it is adapted to an RBC for CAO risk assessment.

Categories of OHA changes post-ATSAC are captured in the “Change Log” tab of “Workbook 1: DEQ Proposed TRVs” and “Workbook 2: TRV Derivation.”

## Section 3 ATSAC Feedback on Workbooks

### Workbook 1: DEQ Proposed TRVs

Workbook version shared with the ATSAC: [Workbook 1 on ATSAC Website](#)

Workbook version shared with the RAC: [Workbook 1 on RAC Website](#)

ATSAC feedback: Look for typo on sheet 1 that now says “acute” where it should say “chronic”

OHA response: *These typos are all corrected.*

1. ATSAC feedback: List out reasons for TRV selection and then just indicate reason/rule applied in the table itself. A key for the reasons for change could be added to the info tab with numbers or letters. Then on each row containing the selected TRV, could just have the number/letter for the applicable rule listed.

OHA response: *OHA drafted a more explicit set of internal processes and policies to follow for selecting one candidate TRV over another in Chapter 2 of the TRV Support Document. In future rounds of TRV updates, OHA can refer to these rules in shorthand in the Workbooks.*

*For this round, OHA applied a similar concept to this workbook to explain cases where a TRV is proposed to change from what was already in rule. OHA standardized the reason for change shorthand that appears in Tabs 3-5 and added a key with a more robust description for each reason to Tab 1.*

### Workbook 2: TRV Derivation

Workbook version shared with the ATSAC: [Workbook 2 on ATSAC Website](#)

Workbook version shared with the RAC: [Workbook 2 on RAC Website](#)

2. ATSAC feedback: Consider combining info from Workbook 1 into Workbook 2 so there is only one Workbook.

*OHA response: OHA decided not to combine workbooks at this stage of the process because DEQ anticipates that most users during the TAC Review and Update Rulemaking will only be interested in the selected TRVs as opposed to all TRV candidates and detailed derivation information. That more detailed information is still available in this Workbook 2: TRV Derivation.*

3. ATSAC feedback: Add POD value (in  $\mu\text{g}/\text{m}^3$ ) and IUR

*OHA response: OHA has added IURs to Workbook 2. For noncancer TRVs, OHA had not already extracted the numerical values for PODs from authoritative source documentation, so adding this would create a significant time delay at this stage. OHA agrees that capturing the POD value is a good idea and will consider including that information in the next round of TRV updates in OHA's continued effort to compile a robust database with key TRV derivation information. The lack of the POD value in the current workbook does not impact the TRV proposals in the proposed rule.*

4. ATSAC feedback: Re-arrange columns to the following order: critical effect, POD value, POD type, POD duration, time adjustment, HEC and dosimetric adjustment (add HEC value), then UFs.

*OHA response: OHA has rearranged columns as recommended, except that OHA was not able to add a column for POD value for noncancer TRVs as explained in response to item #4 above.*

5. ATSAC feedback: When there is a DAF listed as 1, that means that categorically there was an HEC adjustment. OHA has listed "No" for "HEC adjustment" when the DAF was 1. These should be changed to "Yes" because it often explains why a  $\text{UF}_A$  of 3 rather than 10 was used.

*OHA response: OHA agrees and made this correction. This update does not, on its own, change numerical values of any TRVs.*

6. ATSAC feedback: Column heading for new IUR column should say "Authoritative source IUR (units)."

*OHA response: OHA agrees and made this change but omitted "Authoritative" from the header for space.*

7. ATSAC feedback: Need to think of new name for column heading with current heading “Source TRV.” The most accurate name would be something like “TRV calculated from authoritative source IUR at  $1 \times 10^{-6}$  target risk,” but that is too long.

OHA response: *OHA agrees and changed this column header to “Calculated TRV at  $1 \times 10^{-6}$  Risk (units).”*

8. ATSAC feedback: Add columns to indicate:
- The date the data in a row were added to the workbook
  - Whether ELAFs and/or MPAFs need to be applied in RBC derivation

OHA response: *OHA agrees this is useful information and added a column to each row with a “Last Change Date” header. OHA also added a notes column to both workbooks indicating for each TRV whether an MPAF or ELAF needs to be applied when converting that TRV to an RBC in DEQ’s CAO program. OHA also added additional notes in the same column; for example, notes to indicate whether a PPRTV value is a screening level or regular PPRTV and whether the TRV is based on an Authoritative Source draft value among others.*

9. ATSAC feedback: Specify species where we list “animal” vs. “human.”

OHA response: *OHA agrees this is a good idea. Adding that information at this stage of the process would require going back to the authoritative source documentation for each TRV, adding significant time delay to the process. OHA plans to capture this information the next time that TRVs are updated.*

10. ATSAC feedback: Clarify rounding practices.

OHA response: *OHA added a note clarifying that all TRVs are rounded to two significant figures to the info tab on both Workbooks (Tab 1). When calculating or deriving TRVs, OHA used all available digits on inputs to calculations and only rounded for the final TRV. Tabs containing TRVs also include columns that may be hidden showing unrounded values. OHA also added this to Chapter 2 of the TRV Support Document.*

## Additional Improvements to Workbooks

OHA made additional updates to the Workbooks beyond those prompted by ATSAC feedback. Examples include:



- Added Tabs 7 and 8 to Workbook 2: TRV Derivation to show explicit derivations for TRVs for dioxins and furans (Tab 7) and PAHs (Tab 8), including individual congener TEFs and RPFs.
- Added “Change Log” tabs to both workbooks to maintain a running list of updates made over the course of current and future revisions.
- Added column to “Workbook 1: DEQ Proposed TRVs” to show changes made between the ATSAC and the RAC.
- Added more features to the “Information” Tabs on both workbooks, such as:
  - Acronym lists
  - Notes legend
  - Authoritative source information
  - Cross-references to other related resources and materials

## Section 4 ATSAC Feedback on Technical Support Documents

### ATSAC Feedback on Document 1: Overview of TRV Review

Material that was in ATSAC Document 1 is now in Chapter 2 of the TRV Support Document

11. ATSAC feedback: Indicate the number of chemicals considered that ended up without a proposed TRV along with something about plans to keep an eye out/prioritize those for future research/attempts.

*OHA response: OHA added the requested number to a table in Chapter 2 of the TRV Support Document. Chapters 2 and 4 also includes the process for reviewing and updating TRVs for TACs on the Priority List.*

12. ATSAC feedback: Add more about screening algorithm when selecting between multiple options and what criteria were considered when deviating from algorithm, or what criteria agencies used to look outside authoritative sources.

*OHA response: Chapter 2 of the TRV Support Document now contains a detailed description of the processes for selecting TRV proposals when there are multiple options as well as a list of policies applied.*

13. ATSAC feedback: Be clear about target risk for both cancer (1e-6) and noncancer (HQ = 1).

*OHA response: Chapter 2 of the TRV Support Document now includes a list of policies, including this one about target risk.*

14. ATSAC feedback: Maybe include glossary for common terms and abbreviations (TRVs, RfC, non-cancer endpoints, critical effect – especially highlighting where definitions may vary between Oregon agencies, authoritative source, and others.

OHA response: *OHA added an acronym/abbreviation list to the TRV Support Document. Chapter 2 defines the different names that various agencies use for their TRV equivalent values.*

15. ATSAC feedback: Date all docs and be clear about when different phases of review were completed.

OHA response: *Done*

16. ATSAC feedback: Make some kind of statement to specify policy on displaying significant digits/rounding.

OHA response: *OHA added this to the list of policies in Chapter 2 of the TRV Support Document.*

### ATSAC Feedback on Quality Control Document Written by Eastern Research Group (ERG)

ERG's Quality Control Document is now Appendix K of the TRV Support Document

17. ATSAC feedback: Consider drafting an agency document to describe what agencies asked ERG to do, then attach the ERG document to the agency write up.

OHA response: *OHA has followed this request by adding a section to Chapter 2 of the TRV Support Document describing the overall quality control process that then references Appendix K, which is ERG's quality control memorandum.*

### ATSAC Feedback on Document 4: Proposed TRVs where DEQ is the Authoritative Source

Material that was in ATSAC Document 4 is now in Chapter 5 of the TRV Support Document

#### *Section on acute TRVs*

18. ATSAC feedback: Do unit conversions as first step, early in derivation. For example, convert units at POD level prior to any other adjustments. This allows for more direct comparisons between POD and final value. Show unit conversion the same way each time (show molecular weight divided by 24.45 so people can calculate themselves).

OHA response: *This is valuable feedback that OHA will consider for the next round of*

*TRV Updates. OHA did not make any changes based on this comment in this round of updates because it does not change the proposed TRV values themselves and would add time to the current update process.*

19. ATSAC feedback: Statement from ATSAC member: “...when using Haber’s Law, an empirically derived exponent “n” should not be used if the target exposure duration is outside the tested time window in the empirical study.”

*OHA response: OHA agrees with this ATSAC member’s comment and checked all cases where an empirically derived exponent “n” had been applied. OHA only found two:*

- Bromomethane – the study only tested out to 60 minutes. Anything longer than that is an extrapolation. Therefore, OHA used default exponent “n” of 1 rather than the empirically derived 1.33.*
- Propylene oxide – the empirical study OEHHA used to derive exponent “n” only tested out to 7 hours of exposure. Therefore, OHA used default exponent “n” of 1 rather than empirically derived exponent “n” of 1.5.*

20. ATSAC feedback: Do not use final values as PODs when adjusting. Adjust POD and then apply UFs. For example, don’t apply exposure time adjustments to OEHHA 1-hour RELs. Instead, make the adjustment to the POD underlying the OEHHA 1-hour REL and then apply appropriate UF. Math works out the same, but is conceptually inconsistent.

*OHA response: OHA agrees that this would have been clearer and will be more consistent with this in the next round of updates. This ATSAC feedback would not alter the TRV values, so in the interest of timeliness OHA did not make any changes to materials based on this comment for this round of updates but will apply it in the next round.*

21. ATSAC feedback: Include OECD Work Group guidance as a reference

*OHA response: OHA has added the reference to Chapter 5 of the TRV Support Document*

22. ATSAC feedback: Put “Haber’s Law” in quotes since it isn’t actually a law.

*OHA response: This change has been made in the TRV Support Document.*

23. ATSAC feedback: Make clearer in document that exposure durations shown in Table 2 were not actually used in any adjustment. Only time adjustment to intermediate MRLs was to remove the days/week adjustment.

*OHA response: OHA added a sentence below this table explaining that exposure*

*durations were not used in the exposure time adjustments as requested. This new language is incorporated into the new example described in response to the next item.*

24. ATSDR feedback: Include example of adjusting an ATSDR intermediate MRL by removing days/week adjustment (as we did in Table 2) and an example for the same chemical where “Haber’s Law” is used to compress total exposure hours down to 24 hours from the exposure duration in the study. The purpose of this comparison would be to show how the chosen method is more health protective.

OHA response: *Added example after table 2.*

25. ATSAC feedback: Be consistent in specifying what type of DAF is applied.

OHA response: *For the purposes of how OHA used this in rulemaking, OHA used the umbrella DAF term in this document. Workbook 2 does often designate which type of DAF was applied. OHA understands other people might want to use that level of specificity, and next time OHA will ensure to capture that more consistently in the documentation. Each entry links to the source documentation, so the reader can find it if interested in specific type of DAF used.*

26. ATSDR feedback: In Table 1 when POD units are already mass/volume, should just delete the bullet list item for unit conversion, rather than leaving it there with an “NA.”

OHA response: *Change made*

27. ATSDR feedback: In Table 2 – “subchronic TRV” should be changed to “subchronic reference value” to better reflect source nomenclature. In the formula and the table “days/week” should be “days per week adjustment.”

OHA response: *Change made*

28. ATSDR feedback: Where PPRTV is the source, and “RfC” should be abbreviated “p-RfC” to distinguish from EPA IRIS program. See especially ethylene glycol.

OHA response: *Change made*

29. ATSAC feedback: For chemicals in which the endpoint is listed as respiratory and eye irritation, is it confirmed which endpoint the POD is derived from? In some cases (e.g., benzyl chloride, phenol, selenide), both endpoints are listed, and Haber’s Law is presumably being applied even though this should be an exception (for eye and mucous membrane irritation) because the effect would be concentration-dependent and not

time dependent.

OHA response: *OHA added some new language to Chapter 2 section 2.2 and to the paragraph in section 5.1.1 of Chapter 5 of the TRV Support Document explaining how this exception to “Haber’s Law” can be complicated by the cooccurrence of other damage or irritation caused by cellular damage as opposed to trigeminal nerve activation. Eye or mucosal membrane irritation does not mean an automatic exemption from the applicability of “Haber’s Law.” Generally, OHA followed the lead of the authoritative source from which the reference value came. If they applied “Haber’s Law” to adjust exposure time, so did OHA. If not, then neither did OHA. In the case of the three examples mentioned by ATSAC:*

- *Benzyl chloride – target organ is eyes and respiratory irritation, which could meet the criteria for not applying Haber’s Law, but OEHHA applied it in their derivation of their value, which OHA proposes to accept with a time adjustment.*
- *Phenol – Same as Benzyl chloride – eye, nose, throat irritation in human volunteers*
- *Selenide – Caused eye and respiratory irritation in guinea pigs but also caused difficulty breathing and inactivity after exposure. This implies an effect greater than the one that would be triggered solely by activation of the trigeminal nerve, which is the criterion for not applying “Haber’s Law.”*

#### *Section on the use of surrogate TACs to get TRVs*

30. ATSAC feedback: Explore ways to make it easier to follow crotonaldehyde chronic TRV in Workbook 2.

OHA response: *Moved crotonaldehyde from Tab 7 (“References to other TACs”) to Tab 6 (“Appendix Noncancer ALL”) in Workbook 2 where it is easier to find and replaced link to ATSDR’s acrolein derivation information with link to “TRV Support Document” chapter 5, section 3.*

31. ATSAC feedback: Did double check all values for acrolein and all are correct.

OHA response: *Double checked – all acrolein values are correct*

32. ATSAC feedback: Doc 4 Table 3 (surrogates table) – entry for crotonaldehyde – TCEQ’s chronic ReV for acrolein is 2.7 ug/m3 – not 8.1.

OHA response: *Corrected in TRV Support Document Chapter 5*

33. ATSDR feedback: N-Propylbenzene entry in Table 3 – list authoritative sources where DEQ’s proposed values for ethylbenzene come from.

OHA response: *Clarification added on source of DEQ proposed value for both n-propylbenzene and perfluorooctanesulfonamide (PFOSA)*

34. ATSDR feedback: Doc 4 table 3 “TRVs that DEQ Derived by Applying Toxicity Information from a Better Studied Chemical as a Surrogate” should summarize rationale used by source of value for read-across extrapolation, not just cite that the source agency did it.

OHA response: *OHA did not add this information consistently into the table (now located in Chapter 5 of the TRV Support Document) during this round of TRV review, but did ensure that there is a hyperlink to the source material where the rationale can be found.*

### *Section on modified UFs*

35. ATSAC feedback: Consider ways to better describe or make clearer when agencies went outside authoritative sources to look for candidate TRVs.

OHA response: *Added descriptions of the algorithms and policies OHA followed to Chapter 2 of the TRV Support Document.*

36. ATSAC feedback: Table 4 – Chromium III – mention that ATSDR intermediate MRL was selected because no chronic MRL or other chronic value available from authoritative sources

OHA response: *Added this information to the relevant table entry in Chapter 5 of the TRV Support Document.*

37. ATSAC feedback: Delete hexane acute TRV from Chapter 5 (TRVs where DEQ is Authoritative Source) since OHA is proposing to use an updated acute TRV from ATSDR.

OHA response: *Deleted as requested*

38. ATSAC feedback: Wherever a  $UF_L$  is proposed for adjustment from 2 to 3, be careful with language as not all authoritative sources default to 3, most default to 10.

OHA response: *Language removed*

39. ATSAC feedback: For acetone chronic noncancer TRV change  $UF_L$  to 10.

OHA response: *Changed based on recommendation broadly supported by ATSAC members. OHA also clarified policy around UFs in Chapter 2 and Appendix M.*

### *Section on other modifications*

40. ATSAC feedback: Apply the ATSDR intermediate MRL for hydrazine as the acute TRV without time adjustment. Add it to table 2 of Chapter 5 but make the days per week adjustment 7/7, which reduced to a factor of 1. Mathematically this means the acute TRV will be equal to the ATSDR intermediate MRL.

OHA response: *Moved hydrazine to table 2 as recommended and did not apply any time adjustments to the ATSDR intermediate MRL.*

41. ATSAC feedback: Adjust the way boron trichloride equation is written. Make it so the final answer is at the end rather than the beginning.

OHA response: *Equation rearranged as requested*

### *Section and table on PAH RPFs*

42. ATSAC feedback: Add benzo[a]pyrene to Table 5 (now Table 6) with an RPF of 1 and note that it is the index chemical.

OHA response: *Done*

43. ATSAC feedback: Modify notes in “DEQ Notes” column to make sure they don’t imply that we are proposing new RPFs – but rather correcting an earlier error by applying those RPFs to the 2017 IRIS IUR for benzo[a]pyrene rather than the outdated OEHHA IUR.

OHA response: *Content of this note is better communicated in Workbook 1 as “reason for change.” The note was not needed here, OHA deleted it from this location.*

### *Section on TRVs proposed for adoption without modification*

44. ATSAC feedback: Document better what sources other than EPA, ATSDR, and CalEPA lack that causes them to not be considered authoritative. Document decision tree for going to alternate sources maybe in introductory/overview materials.

OHA response: *Authoritative Sources are listed in rule. The EPA, California EPA, and ATSDR were originally selected as authoritative in rule because of their consistency and transparency in methods and the robustness of their systematic review process. Their policies around uncertainty factors also consistently align with OHA’s. Other states and jurisdictions also do some good work, but OHA needs to more carefully review derivation methods and application of uncertainty factors to verify that they are congruent with OHA policies. OHA added information on this topic to Chapter 2 of the TRV Support Document.*

45. ATSAC feedback: Make clearer in workbooks where these TRVs are sourced from.

OHA response: *These derivations can be quite variable. OHA adjusted the source link in Workbook 2 when DEQ is the authoritative source to reference the TRV Support Document where full derivation details, including the original source, are available.*

46. ATSAC feedback: Add more description around why these sources were considered of “adequate derivation quality.”

OHA response: *Added more description of these other sources to the paragraph introducing Section 6 of Chapter 5 in the TRV Support Document.*

#### *General feedback on Document 4*

47. ATSAC feedback: Add table summarizing UF defaults for various agencies.

OHA response: *Table added to Appendix M of this TRV Support Document.*

#### **ATSAC Feedback on Document 5: Grouping of Chemicals**

Material that was in ATSAC Document 5 is now in Chapter 3 of the TRV Support Document

48. ATSAC feedback: Specify in section 4.1 that metals and compounds do not include organometallic compounds. Proposed language from minutes “metals and inorganic compounds”

OHA response: *OHA kept the names of most metal groups as “metal and compounds” but did change arsenic and mercury to “metal and inorganic compounds.” The inorganic designation is most important for these two metals because organic arsenical compounds (often found in fish) are typically less toxic than inorganic arsenic compounds, and organic mercury compounds are typically more toxic than inorganic compounds but are not typically released to air.*

49. ATSAC feedback: For Toluene diisocyanates - Correct information in “Difference in approach from existing rule” column needs to be corrected: “Additionally, in Section 2, Table 1, the entry for toluene diisocyanate (TDI) isomers (CAS: 26471-62-5) in column 3 (Difference in approach from existing rule) needs to be corrected. The OEHHA REL listing covers mixed TDI isomers, 2,4-TDI and 2,6-TDI as a group, not separately.” From minutes “neither ATSDR nor OEHHA distinguish between isomers.

OHA response: *Corrected note as requested*

50. ATSAC feedback: In future, note how our proposed groupings are similar or differ from groupings used by authoritative sources.



OHA response: *OHA will strive to make this clearer for the next round of updates. Generally, when OHA changed a grouping, OHA provided reasoning from authoritative source when proposing a change to grouping practice.*

51. ATSAC feedback: CalEPA has an RfC for sulfuryl fluoride. If this fluoride compound is an issue in Oregon, it should be included.

OHA response: *Added sulfuryl fluoride to TRV list with acute and chronic noncancer TRVs from CalEPA Division of Pesticide Regulation (DPR). OHA did not include this with Fluoride and inorganic compounds because sulfuryl fluoride specifically has its own TRV separate from other fluoride compounds.*

52. ATSAC feedback: Silica feedback- in the meeting there was some discussion of whether 4 microns in diameter was the right size fraction for crystalline silica. Ultimately, ATSAC agreed that the proposal was consistent with the science and the practice among agencies around the country. Written follow-up from ATSAC confirmed this.

OHA response: *OHA did not take any action based on this feedback.*

53. ATSAC feedback: WHO TEF question- OHA asked ATSAC whether to keep the World Health Organization's (WHO's) 2005 toxic equivalency factors (TEFs) for dioxins and furans or to adopt the 2022 updated WHO TEFs. ATSAC member responses were mixed: Two members favored adopting the 2022 TEFs, while two recommended keeping the 2005 ones unless another agency or OHA could do a more thorough evaluation of the 2022 TEFs. The fifth ATSAC member favored adopting the 2022 TEFs if an independent assessment could be done. (See Appendix E)

OHA response: *Since ATSAC had their discussion, ATSDR (one of DEQ's Authoritative Sources) has formally adopted the 2022 WHO TEFs. Also, the OHA staff working on CAO asked another OHA toxicologist that is not part of the CAO team to independently evaluate the 2022 WHO TEFs. That staff member's response is available as Appendix S in this document. Both of these independent efforts indicate that the 2022 WHO TEFs are a great improvement over the 2005 TEFs and are based on a much more robust set of data and methods.*

## ATSAC Feedback on Document 6: Proposed TRVs using Screening PPRTVs as the Authoritative Source

Material that was in ATSAC Document 6 is now in Chapter 4 of the TRV Support Document

54. ATSAC Feedback: Formic Acid- Recommendation for DEQ to consider applying a composite uncertainty factor (UF) cap of 3,000 to the PPRTV derivations and adjusting the UF values where necessary. In the case of formic acid's screening PPRTV, an ATSAC member recommended decreasing the  $UF_s$  and  $UF_D$  from 10s to 3s, which would reduce the overall UF from 10,000 to 3,000 (the calculated total UF is 30,000 but screening PPRTVs cap at 10,000)

*OHA response: OHA agrees that there is a high level of uncertainty in a screening PPRTV with a total UF of 30,000. As a result of this ATSAC feedback, OHA is now proposing a new policy, which is to only use screening PPRTVs when the total UF is 3,000 or below (see Chapters 2 and 4 in the TRV Support Document for more description). OHA had proposed a noncancer chronic TRV for formic acid to ATSAC, but OHA is no longer proposing this TRV (see Chapter 4 of the TRV Support Document). Currently, formic acid does not have any proposed TRVs, which is consistent with existing 2018 Rule.*

*OHA is not proposing to adjust screening PPRTV UFs to achieve a total UF of 3,000 because one of OHA's other policies on UFs is:*

*"OHA's default approach to uncertainty factors is to adopt the factors applied by the EPA, ATSDR, or CalEPA. OHA may modify UF for time adjustment purposes (e.g., adjusting from an intermediate ATSDR MRL to a chronic TRV) or when the candidate value is from a source other than EPA, ATSDR, or CalEPA" (excerpt from Chapter 2 of the TRV Support Document).*

*This policy on UFs is consistent with ATSAC feedback on 1-methylnaphthalene (see Appendix R for ATSAC feedback on 1-methylnaphthalene as well as Chapter 6 in the TRV Support Document).*

55. ATSAC Feedback: Requested the addition of a flag on TRVs that are screening level PPRTVs so they can be prioritized for updates when something more robust becomes available

*OHA response: OHA agrees with this suggestion and have added a column ("TRV notes") to the Excel workbooks that indicates if a TRV proposal is based on a screening PPRTV. In addition, OHA continues to share and update a separate written summary of the cases where OHA is proposing to use a screening PPRTV as the TRV (see Chapter 4 in the TRV Support Document).*

## **ATSAC Feedback on Document 7: Proposed TRVs Not Yet Finalized by Authoritative Sources**

Material that was in ATSAC Document 7 is now in Chapter 4 of the TRV Support Document

56. ATSAC Feedback: Requested the addition of a flag on TRVs to more clearly identify the TRVs based on draft values from authoritative sources as well as additional documentation of the date of the draft TRV was published in the workbooks.

*OHA response: OHA agrees with this suggestion and added a column (“TRV notes”) to the Excel workbooks to indicate if a TRV proposal is based on a draft TRV that is not yet finalized by an authoritative source. The “TRV Publication Date” column in the Workbook 2 tabs reflects the date the draft TRV was published by the authoritative source. For example, the draft benzene noncancer chronic TRV from ATSDR was published on 10/1/2024 and this is the “TRV publication date” listed in Workbook 2. OHA also continues to share and update Chapter 4 in the TRV Support Document, which includes a section that tracks which TRVs authoritative sources become final during this Rulemaking.*

57. ATSAC Feedback: Recommended reviewing public comments received by authoritative sources on the proposed TRVs not yet finalized by the authoritative sources. If the public comments are not readily available, the ATSAC member recommended reaching out to ATSDR, OEHHA, or US EPA to ask to see the public comments.

*OHA response: OHA agrees that there are certain situations where it would be helpful to look at public comments submitted to authoritative sources. OHA added a new paragraph to Chapter 4 to describe the situation in which OHA staff would try to get access and read public comments submitted to authoritative sources. Specifically, OHA will continue to closely monitor TRV proposals from authoritative sources that become final during DEQ’s Rulemaking. If there is a change between the draft and final TRV from an authoritative source, then OHA staff will work to understand why there was a change and will closely look at all available TRV documentation, including public comments. OHA will reach out to staff at the authoritative sources if key TRV documentation is unavailable publicly and/or the source of the TRV change is unclear. OHA will summarize findings on authoritative source TRV changes in the TRV Support Document.*

*For additional context, OHA found that all ten of the TRVs that were not yet finalized by authoritative sources at the time of the ATSAC meetings, have since been officially finalized by the authoritative source (See Chapter 4 in the TRV Support Document, Table 4-2). None of these ten TRVs changed between the public comment version and the final version published by the authoritative source.*

58. ATSAC Feedback: More clearly document the plan for adjusting TRV proposals when authoritative sources finalize draft TRVs, especially if the public comments on the draft authoritative source documents result in changed authoritative source TRVs

OHA response: *OHA added information on the plan to update TRV proposals from draft to final to Chapter 2 of the TRV Support Document. In addition, OHA clarified this process in Chapter 4 of the TRV Support Document, which is the chapter where OHA discusses and lists the draft TRVs in detail. As described in #53 above, if there is a change between the draft and final TRV from an authoritative source, then OHA staff will work to understand why there was a change and will closely look at all available TRV documentation. OHA will summarize findings on authoritative source TRV changes in the TRV Support Document.*

59. ATSAC Feedback: An ATSAC member recommended retaining OEHHA acute REL for acrolein rather than the draft ATSDR value. He documented his rationale in the ATSAC written response compiler.

OHA response: *OHA agrees that OEHHA used the geometric mean of two studies, which makes value more scientifically robust. ATSDR didn't cite the Darley study. OHA supports using the OEHHA acute TRV for acrolein rather than the more recent ATSDR acute MRL.*

## Section 5 General ATSAC comments

60. ATSAC feedback: Toluene chronic TRV – ATSAC members recommended OEHHA 2020 value over ATSDR value because of more modern POD extrapolation method. Also recommended generally considering POD extrapolation methods in addition to recency of underlying science when selecting TRVs. ATSAC members also noted that the OEHHA documentation also cited the same studies ATSDR used and had the more recent comprehensive look at the available science.

OHA response to ATSAC: *OHA agrees with ATSAC's recommendation to use OEHHA's chronic REL for toluene instead of ATSDR's chronic MRL. The OEHHA value reflects more modern POD derivation methods than other candidate values as well as the most recent review of the scientific literature. This change has been made in Workbooks 1 and 2.*

61. ATSAC feedback: 1-Bromopropane chronic TRV – ATSAC member recommends OEHHA value rather than ATSDR because it represents the more recent comprehensive evaluation of available science.

OHA response to ATSAC: *OHA agrees with the ATSAC member comment and now proposes to use OEHHA's chronic REL as the chronic noncancer TRV for 1-bromopropane. This change has been made in Workbooks 1 and 2.*

62. ATSAC feedback: Methanol chronic TRV – ATSAC member recommended OEHHA value. “There is not enough information about the PBPK model from the 2013 IRIS document, but based on the number of datasets available, I would not expect a very good or robust PBPK model for methanol. It also seems that BMDL-1SD was used for the inhalation RfC while OEHHA used BMCL05. I prefer OEHHA value unless the PBPK model is very strong.”

*OHA response to ATSAC: OHA agrees with ATSAC’s recommendation to use the OEHHA chronic REL for methanol rather than the IRIS RfC. The OEHHA value is based on a more health-protective benchmark response (BMR) (5% versus 1 standard deviation) POD and does not rely on a PBPK model that cannot be adequately evaluated for quality as does the IRIS RfC.*

63. ATSAC feedback: 2-Butanone chronic TRV – ATSAC member agreed with the acute value for this TAC but pointed out that it is lower than all candidate chronic TRVs for that TAC. The ATSAC member suggested changing the chronic value to match the acute or choose not to have a chronic TRV.

*OHA response: OHA proposes to delete the chronic noncancer TRV for 2-butanone because it is higher than best available acute TRV. Monitoring efforts that include chronic evaluations of 2-butanone should compare the long-term monitoring results to the acute TRV. This is the same approach ATSDR followed with naphthalene and which OHA is proposing to emulate. OHA also proposes to adopt this as a general policy: When all candidate chronic noncancer TRVs are higher than the acute TRV for a given TAC, do not adopt a chronic TRV for that TAC and use its acute TRV in its place.*

64. ATSAC feedback: Trivalent chromium acute TRV – ATSAC members made conflicting recommendations for this TRV at different times. At one time an ATSAC member recommended adopting the more recently published OEHHA 1-hour REL with exposure time adjustments because it was more recently published. At another time, the ATSAC member recommended using an exposure time adjusted ATSDR intermediate MRL as OHA originally proposed to ATSAC because it is based on a portal of entry effect and because there is less uncertainty extrapolating down from a subchronic study down to 24 hours than extrapolating from the 30-minute experimental exposure the OEHHA value is based on up to 24 hours. A second ATSAC member also endorsed the use of ATSDR’s intermediate MRL.

*OHA original note for the acute TRV for trivalent chromium: DEQ proposes an acute TRV based on ATSDR’s intermediate MRL rather than OEHHA’s more recently published acute REL because OEHHA’s value is based on a much older critical study than ATSDR’s intermediate MRL and because an exposure time adjustment to OEHHA’s 1-hour REL*

*would create an acute TRV lower than the proposed chronic TRV.*

*OHA response to ATSAC: OHA proposes to stay with the originally proposed acute TRVs for trivalent chromium based on ATSDR's intermediate MRLs because they require a less extreme exposure time adjustment and are based on portal of entry effects in the upper respiratory system which are relevant for acute inhalation exposures in humans. There were also more members of ATSAC favoring this approach.*

65. ATSAC feedback: Be aware that TCEQ uses a different methodology for chemicals with an extra thoracic port of entry effect (DAF equals 1 rather than minute of ventilation divided by surface area). This is different than how Authoritative Sources listed in DEQ rule do it. So be aware, when adopting TCEQ values, whether this methodological inconsistency with other authoritative source is in play. ATSAC members stated that there didn't appear to be any cases of this inconsistently affecting any proposed TRVs sourced from TCEQ in this round of updates.

*OHA response: OHA appreciates this feedback and will make a note to watch out for cases like this in future rounds of TRV updates. As this did not apply to any proposed TRVs this time around, OHA did not make any changes based on this recommendation.*

## Section 6 Errors found and corrected by OHA staff

### Table numbering error

Fixed

### Boron trichloride

Both the acute and chronic noncancer TRVs for boron trichloride are based on the TRVs for hydrogen chloride (hydrochloric acid). In preparation for ATSAC meetings OHA adjusted many 1-hour RELs from OEHHA to account for differences in exposure time. The acute TRV for hydrochloric acid was one of the those that OHA adjusted for exposure time differences between OEHHA and OHA (see TRV Support Document: Chapter 5, Section 2.2). Prior to ATSAC meetings, OHA had not updated the acute TRV for boron trichloride to account for the exposure time adjustment applied to hydrogen chloride. OHA staff discovered and corrected this error after ATSAC meetings had ended (see TRV Support Document: Chapter 5, Section 5).

### Crotonaldehyde

OHA discovered that the chronic TRV for crotonaldehyde was incorrect. OHA calculated the chronic TRV for crotonaldehyde by applying an RPF derived by TCEQ to the chronic TRV for acrolein. Between the time OHA staff calculated the TRV for crotonaldehyde and the

ATSAC meetings, ATSDR had updated their chronic MRL for acrolein, and OHA proposed to adopt it. However, OHA staff did not update the chronic TRV for crotonaldehyde based on the new TRV for acrolein prior to the ATSAC meeting. OHA discovered and corrected this error after the ATSAC meetings had ended by updating the crotonaldehyde chronic noncancer TRV to reflect the selection of ATSDR's chronic MRL for acrolein (see TRV Support Document: Chapter 5, Section 3).

## N-Propylbenzene

OHA concluded that the rationale for using ethylbenzene as a surrogate for n-propylbenzene did not extend to the cancer TRV. While EPA's PPRTV program did consider ethylbenzene a good surrogate for noncancer risks, they were silent on the carcinogenicity of n-propylbenzene.

## Section 7 Responses to ATSAC on additional topics covered elsewhere

There were some TRVs that OHA talked about with ATSAC either in email threads outside of meetings or in special meetings focused on specific TACs (Table A-2).

**Table A-2.** Summary of where to find ATSAC feedback and OHA responses on specific TACs not covered in ATSAC meetings on the TRV proposals (meetings #4-7).

| Toxic Air Contaminant           | ATSAC Feedback                                                  | OHA Response                                                                           |
|---------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Brominated dioxins and furans   | Email exchange documented in Appendix R of TRV Support Document | TRV Support Document Chapter 3: Groupings of Chemicals (Section 3.1)                   |
| Diesel Particulate Matter       | Appendices F and I                                              | TRV Support Document Chapter 6: Agency Highlighted TRVs (Section 1)                    |
| Manganese: Acute TRV            | Appendices C and G                                              | Appendix Q: DEQ Manganese Acute TRV Proposal Memorandum                                |
| 1-Methynaphthalene: Chronic TRV | Email exchange documented in Appendix R of TRV Support Document | TRV Support Document Chapter 6: Agency Highlighted TRVs (Section 2)                    |
| Perfluorodecanoic Acid (PFDA)   | Email exchange documented in Appendix R of TRV Support Document | TRV Support Document Chapter 5: TRVs Where DEQ is the Authoritative Source (Section 5) |

# **Appendix B: Meeting Minutes for ATSAC Meeting #2 on the TRV Selection Process**



# Air Toxics Science Advisory Committee (ATSAC)

*Meeting 2: January 20, 2023, 1-4pm PT*

## *Meeting Minutes*

### Meeting Attendees

| ATSAC Members          |                                                               |
|------------------------|---------------------------------------------------------------|
| Jefferson Fowles       | California Department of Public Health/New Zealand Government |
| John Budroe            | California Environmental Protection Agency (retired)          |
| Qiaoxiang (Daisy) Dong | California Environmental Protection Agency                    |
| John Vandenberg        | Duke University                                               |
| John Stanek            | Environmental Protection Agency                               |
| Susan Tilton           | Oregon State University                                       |
| Jessica Myers          | SRC Inc.                                                      |
| Project Team           |                                                               |
| Matthew Davis          | Oregon Department of Environmental Quality (DEQ)              |
| Apollonia Goeckner     | Oregon Department of Environmental Quality (DEQ)              |
| J. R. Giska            | Oregon Department of Environmental Quality (DEQ)              |
| Kristen Martin         | Oregon Department of Environmental Quality (DEQ)              |
| Susan MacMillan        | Oregon Department of Environmental Quality (DEQ)              |
| Holly Dixon            | Oregon Health Authority (OHA)                                 |
| David Farrer           | Oregon Health Authority (OHA)                                 |
| Facilitation Team      |                                                               |
| Ben Duncan             | Kearns & West                                                 |
| Angela Hessenius       | Kearns & West                                                 |

### Welcome and Introductions

Ben Duncan, Kearns & West, opened the meeting, facilitated introductions from the project team (Oregon Department of Environmental Quality (DEQ) and Oregon Health Authority (OHA)) to introduce themselves, and conducted roll call of Air Toxics Science Advisory Committee (ATSAC) members. Ben reviewed the meeting agenda, which included 1) Finalizing the Charter, 2) Discussion of Authoritative Sources, 3) Presentation and Discussion of Proposed Process for Chronic and Acute Toxicity Reference Values (TRVs), 4) Presentation on TRV Workflow, and 5) Closing and Next Steps.

### Finalizing the Charter

Ben reviewed the changes made to the ATSAC operating principles based on the feedback heard from the individual ATSAC member interviews with Kearns & West. Two modifications were made to the operating principles: an additional process step for dialogue and deliberation was added to the framework for identifying agreement and the language was changed to one of the ground rules to limit the discussion to health risk assessment rather than to health science. ATSAC members approved the final operating principles, which have been added to the committee's charter.

## Authoritative Sources

Holly Dixon, OHA, and Matt Davis, DEQ, gave a presentation on authoritative sources and the process for selecting TRVs and Ben facilitated discussion on specific questions for feedback from ATSAC members. Holly defined the key lists that the group will discuss. The first was the Priority Toxic Air Contaminants list (“priority list”), which includes over 600 chemicals that are reportable in the Cleaner Air Oregon program. All permitted facilities need to report on these emissions as part of a statewide emissions inventory exercise every three years. DEQ manages and updates this list. During the TRV review process, the project team will be looking for TRVs that apply to the chemicals on this list.

Matt shared that the project team envisions two primary bodies of work for DEQ and OHA during the TRV review process. The first body of work is to review the chemicals on the priority list that already have recognized TRVs to see if any of the authoritative sources have updated these values. The second body of work is to review the chemicals on the priority list that do not currently have TRVs to see if any of the authoritative sources have adopted values that the project team can consider adding to the Cleaner Air Oregon program.

Matt also shared the rationale for the project team’s proposed framework for TRV review. Given the practical limitations of DEQ and OHA’s staff capacity, the project team plans to use existing values from the authoritative sources as their primary body of evidence for selecting TRVs. Their goal is to develop a hierarchy or algorithm that will be used for all the chemicals on the priority list to evaluate any changes that authoritative sources have made and prioritize which TRV updates should be proposed. In some cases, none of the authoritative sources have existing values or have made updates. The project team expects that the ATSAC will focus on certain chemicals for deeper discussion. Matt noted that the authoritative sources and current TRVs are listed in Oregon Administrative Rule (OAR). DEQ does not have authority to change rules; they must work with an independent rulemaking commission, the Environmental Quality Commission (EQC). This rulemaking process will occur following the project team’s work with the ATSAC and generally takes about a year to complete. Given these constraints, the project team has proposed an approach that relies on authoritative sources and does not include a deep dive into every individual chemical.

Matt outlined that the focus of this meeting is on a couple key process questions before the ATSAC begins discussing particular chemicals. These questions include the following: 1) What information should the agencies consider when evaluating work from other organizations as the agencies work to establish TRVs when the authoritative source is DEQ in consultation with the ATSAC? 2) What process should the agencies use to evaluate updated TRVs from the authoritative sources?

John Vandenberg asked whether the ATSAC will have a role in identifying or suggesting other contaminants to include on Oregon’s priority list. Matt shared that the chemicals on the priority list are also in rule and require a rulemaking to add to. The agencies are considering whether there are chemicals that have TRVs from authoritative services that should be added to the priority list. Providing input on chemicals to add to the priority list is possibly a role for the ATSAC, but the agencies have internal work to do first to decide to what extent they will take on adding new chemicals to the priority list. Holly added that if any ATSAC members have any suggestions for specific chemicals to pay attention to or resources to share, that input would be greatly appreciated by the project team.

Next, Holly outlined the list of authoritative sources that DEQ is directed to rely upon, which is designated in Oregon administrative rule. These rules are adopted by the EQC. The authoritative sources are the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency (EPA), California Environmental Protection Agency (CalEPA), and DEQ in consultation with the ATSAC. Holly noted that in 2021, the EQC added DEQ in consultation with the ATSAC to the list of authoritative sources, which gives DEQ more flexibility in the TRV process. This means that DEQ in consultation with ATSAC can develop TRVs and consider TRVs developed by organizations other than U.S. EPA, U.S. ATSDR, and CalEPA. However, for several reasons, the agencies primarily rely on those three authoritative sources. Holly highlighted that these sources go through extensive peer-reviewed processes to establish TRVs using the best available science and research. For each chemical, expert panels review hundreds of scientific studies to evaluate the weight of scientific evidence, and this public process requires substantial investments of tax dollars. Additionally, regularly establishing new TRVs is beyond the capacity of agencies in Oregon. To establish new TRVs, Oregon would have to undergo a rigorous and costly process. In many instances, the results of a state level review would likely confirm the conclusions of the other authoritative sources.

Since developing a TRV is very resource intensive, the project team plans to look for TRVs beyond US EPA, ATSDR, and CalEPA only if all of the following criteria are met: 1) none of the authoritative sources have a value, 2) the chemical has a high likelihood of harming public health in Oregon, 3) there is adequate scientific information available, and 4) there is agency staff bandwidth. Due to limited resources, the project team's first preference is to look at TRVs from another state or country. These values could be modified, if necessary. In cases where the agencies in consultation with ATSAC look at TRVs developed by an organization not on the authoritative source list, they will check to make sure that the other organization's selection of points of departure and application of uncertainty factors are congruent with the approach taken by Oregon's three main authoritative sources. If not completely congruent with that approach, the project team could still use portions of that agency's work but make some modifications to point of departure selection or uncertainty factor application to make it more consistent. The project team expects to consult with ATSAC members for assessment and application if they pursue this type of work.

Jessica Myers asked how the project team intends to handle the fact the values may be orders of magnitude different between the three authoritative sources, since each use different methods? Holly noted that while there are differences between the three sources, there are also a lot of similarities, and that they will discuss this question in more detail during the portion of the meeting when the group reviews and discusses the proposed process for selecting acute and chronic TRVs. Jessica noted that the same methodology considerations for the authoritative sources will also apply to the other sources, and that it is important for the group to consider this up front.

**Discussion Question: What should DEQ and OHA consider when reviewing values from other organizations or agencies not listed as an authoritative source?**

- Jessica Myers: Jessica shared that in her opinion, Texas Commission on Environmental Quality (TCEQ) has some great values, including for manganese. There are also other states that develop their own values, including Michigan and New York. Jessica shared that it is important to classify state agencies above other non-governmental sources that may have bias in developing those values. Additionally, Jessica suggested that DEQ and OHA look at sources that are using the

methodology that they want to drive these values, because even the methods between the three authoritative sources can be very different.

- John Vandenberg: Some of the considerations should include whether the other organization or agency has published their methodology for their assessments. It is important to have that reference to make sure there is consistency with the values from the authoritative sources. Having a public comment as part of the process of developing those values is also essential. John suggested focusing on other agencies rather than non-governmental organizations (NGOs) whose process and motivations may be less clear. John also pointed out that newer values may not necessarily be better. If there are competing values, John suggested that DEQ and OHA should try to understand why they are different and whether one is more consistent with Oregon's approach.
- John Budroe: John agreed that availability of the methodology and specific derivation that is used for a chemical as well as public comment and peer review should all be transparent. Additionally, John shared that the health value should be based on actual adverse health effects. Some health values are based on other factors such as odor perception, for example.
- Jefferson Fowles: Jeff agreed with other ATSAC members' points and added that it is important to ensure that other agencies' values that are adopted are de novo derived values through their own authoritative process based on primary data, not adopted from another source.
- Susan Tilton: Susan echoed the importance of considering and understanding the methodology for the other values and allowing input on those values through a public comment period.
- Daisy Dong: Daisy suggested that DEQ should develop guidance since different agencies may base their analyses on the same studies but apply different criteria. She noted that even within CalEPA, different branches (e.g., the Department of Pesticide Regulation (DPR) vs. the Office of Environmental Health Hazard Assessment (OEHHA)) use different methods such as uncertainty factors. DEQ and OHA may need to develop criteria that are more conservative or science based. Daisy also noted that even within the authoritative sources, some of the most recent science might not be incorporated. This committee could help the agencies create this guidance so Oregon can develop their own criteria, which should guide the values that are chosen.
- John Stanek: John shared that when looking at the availability of reference values for hydraulic fracturing, they came up with a similar approach using criteria and searchable databases. In their report, there is an extensive appendix with sources that might be available, though this process was based on oral rather than inhalation reference values. Potential alternative sources could be listed there for values that cannot be found elsewhere. For example, the World Health Organization (WHO) has databases for some reference values. This report could be considered as a resource that outlines an approach that was used for over 1,000 chemicals.
- John Vandenberg: As Jessica mentioned, some of the authoritative sources will have quite different values. In these instances, Oregon could choose the lower value, which would be more health protective, in the face of uncertainty about what value to choose. John emphasized that this is a policy choice rather than a science choice.
  - Matt acknowledged that this group is not a decision-making body, but it is appropriate for this group to discuss the application of health science at the interface of science and policy.
  - John added that the methods that are used often delineate science policy choices that have been made during an assessment process. Other agencies often develop set

guidelines for risk assessment that outline the science policy decisions that have been made. The end decision is informed by the policy choices made along the way.

## Proposed Process for Chronic and Acute Toxicity Reference Values

Next, Holly presented the proposed processes for selecting TRVs from the authoritative sources, and Ben facilitated the ATSAC members' responses to the prepared discussion questions. DEQ uses the term TRV when referring to any similarly derived health-based toxicity value. Both acute and chronic TRVs are defined in OAR. For Oregon DEQ, acute refers to exposure to a toxic air contaminant over a 24-hour period and chronic refers to exposure to a toxic air contaminant over a one-year period for noncarcinogens and a lifetime of exposure for carcinogens. DEQ has used and proposes to use different processes for selecting chronic TRVs and acute TRVs.

### Chronic TRVs

| Agency Name                                                   | Name of Chronic TRV                    | Type of TRV Available |
|---------------------------------------------------------------|----------------------------------------|-----------------------|
| U.S. Agency for Toxic Substances and Disease Registry (ATSDR) | Chronic Minimal Risk Level (MRL)       | Noncancer             |
| U.S. Environmental Protection Agency (EPA)                    | Inhalation Unit Risk (IUR)             | Cancer                |
|                                                               | Reference Concentration (RfC)          | Noncancer             |
|                                                               | IUR                                    | Cancer                |
| California Environmental Protection Agency (CalEPA)           | Chronic Reference Exposure Level (REL) | Noncancer             |
| Oregon DEQ in consultation with ATSAC*                        | TRV                                    | Noncancer and Cancer  |

Holly shared a table that includes the authoritative sources and chronic TRV names. Holly pointed out that within the EPA, DEQ and OHA look at values from the Integrated Risk Information System (IRIS) and the Provisional Peer Reviewed Toxicity Values (PPRTV). Within CalEPA, the agencies look at values from the Office of Environmental Health Hazard Assessment (OEHHA). Holly added that the project team welcomes feedback from ATSAC members on other values within the EPA or CalEPA that they should look at. The authoritative sources all assume the same exposure time when developing their chronic TRVs.

The process to select a TRV from the authoritative sources when more than one TRV is available is not in rule. In the past, the agencies chose to select the most recently published TRV from among the authoritative sources. For example, the agencies would select a TRV developed in 2018 compared to one developed in 2010. DEQ and OHA propose to use this same selection approach for chronic TRVs in this TRV review to ensure that the TRVs are based on the most recent review of scientific studies by an authoritative source.

### Discussion Question: What questions or feedback do you have on the general process of selecting the most recently published chronic TRV?

- Jessica: ATSDR has an intermediate value also, which means that they do not typically use subchronic studies to develop chronic number because the subchronic studies would be used for the intermediate values. However, EPA consistently uses subchronic studies, so the durations from these sources are going to be slightly different depending on the data available.

- John Stanek: No comments at this time.
- Susan Tilton: When these values are being compared and there is a difference in the most recent value, are you aware of what is contributing to this difference? Is it because there is new data available? Has the methodology changed?
  - David Farrer, OHA, acknowledged that as ATSAC members have shared, there are differences even within an agency in the approach that they take to develop a reference value. The project team has been looking at many values from many sources at the same time through a comprehensive process, and David observed that the biggest predictor of differences appears to be the era during which the assessment was conducted. For example, an EPA Integrated Risk Information System (IRIS) reference concentration developed in 1991 probably used a different method than EPA IRIS would from 2023. Benchmark dose modeling is a good example. In the 1990s, all the sources were using No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) as points of departure. Over time, across all agencies, there was a clear preference to move towards benchmark dose modeling, and nowadays, all the agencies' first choice is to use benchmark dose modeling if they can. For David, this was an argument in favor of using the most recently published study. At any point in time, there are more similarities than differences across the agencies' methods, but the pace of keeping up with the reviews of agencies differs.
  - Susan added that if the focus is on improvements in the methodology, then there is a good rationale for focusing on the most recently published data. She emphasized the importance of understanding why there are differences rather than automatically using the most recent data.
- Jefferson Fowles: Jeff suggested that it would be helpful to be aware of whether the difference in value is due to the study, the endpoint selected, the point of departure, the benchmark dose, or an uncertainty factor difference, which has been applied differently by different organizations. It would be helpful if there were a categorical way to quickly triage the differences. If there's a new study, then that raises the need to dig into the weeds compared to whether there is a methodological difference that is known across different agencies.
- John Budroe: First, John clarified whether recently published TRVs include both cancer and noncancer values, and the project team answered yes. John then provided an example of ethylene oxide. Both EPA and TCEQ have very recent evaluations based on the same general dataset with dramatically different opinions on how that data should be modeled, resulting in a three order of magnitude difference between the cancer potencies. In this case, it would be necessary to investigate the details of both evaluations to figure out which value to select.
- Daisy Dong: Daisy asked whether the project team will present the ATSAC with all the TRVs that are found from different sources, or only the value that they think is the most reasonable? Daisy agreed with other ATSAC members that the value selected depends on what endpoint is used and what methodology and type of modeling is employed in the study. When there are multiple TRVs that are all scientifically justified, the decisions should be based on which criteria Oregon wants to use. Daisy also suggested that DEQ and OHA look for values developed by the DPR within CalEPA, which has different values than OEHHA, as well as the Office of Pesticide Programs (OPP) within EPA, which has different values than IRIS. Daisy thinks that it would be better if the project team presents the all the TRVs that they can find and let the ATSAC help

them decide which one to choose, rather than only sharing the study and value that the project team initially chooses. That would allow the committee to look at all the selection criteria and then make a recommendation to the project team.

- John Vandenberg: John agreed with other ATSAC members that the most recently published TRV should not be selected automatically and that it is important to evaluate what the differences are across the studies. John agreed with David Farrer's point that the methodologies for some areas have changed and with John Budroe's comment pointing out that different authoritative organizations can have very different values. John felt that it would be a mistake to take the most recent value automatically. If there are different values for different authoritative sources, that requires an evaluation.

Matt reflected that he is hearing from the group that the approach of using the most recently published TRV could be used as the first step in a stepwise process that would help the project team identify chemicals that need a deeper investigation into differences in methodology. Matt sought confirmation from the group that this is an accurate characterization of the discussion that identifying the most recently published TRV is an important step but should not be used as the sole decision-making framework. ATSAC members confirmed that this is an accurate summary of feedback. It can be helpful for screening values and looking at as a starting point, but should not be taken automatically. If there are multiple sources, what are those multiple sources and why are they different are key questions that need to be determined. Which one follows the guidelines more closely to what Oregon DEQ would develop, or which one is more protective of public health?

David asked the group if the recency takes on more importance if there is a greater gap between the newer study and the older study. Perhaps if they're only a couple of years apart in the same period of peer-reviewed literature, it might be more important to look in more detail at the two studies. John Vandenberg shared that renewed assessments of IRIS values did not substantially change the value for most chemicals nor were the new values consistently higher or lower. While the benchmark dose modeling is superior to using a NOAEL and LOAEL, the results are often not that different in application.

Daisy asked whether if there is only a very old TRV available, are the agencies going to update the TRV using the newer methodology? John Budroe shared that most of the older health values are updated when a new dataset becomes available. If there are TRVs that have not been updated since the 1980s or 1990s, it is often because there is no new data to generate a new health value from. John Vandenberg agreed that many of the older IRIS assessments have not been a priority to update since there have not been any new studies. Resources tend to go to conducting assessments of other chemicals that the agency regulatory programs are prioritizing.

In response to these questions and comments, Matt referred back to the criteria that the project team introduced, which determine when the agencies will take a deep dive into specific chemicals with this committee versus not. One of those criteria is that none of the authoritative sources have a value. Another way to frame Daisy's question is whether these are the right criteria, or whether there should be a temporal cutoff. Matt reminded everyone that the group is discussing when they are willing to rely on a value understanding that there are limitations, versus when something should be designated for deep review by agency staff in consultation with this group with the understanding that it will not be possible to do that level of review for all the chemicals.

Daisy shared that DPR updates the reference concentrations after a certain time threshold to be protective of public health. Using a different methodology (e.g., using benchmark dose modeling rather than a NOAEL or LOAEL) yields different values. Daisy also shared that for inhalation, EPA developed new guidance in 2012 for portal-of-entry effects, which increases rather than lowers TRV when using that guidance compared to the previous methodology. There is also a potential to be challenged by the public for not using the most recent methodology and science. EPA also came out with new modeling software for particles to calculate the human equivalent concentration. Given these advancements in methodology, the value could be completely different even if an assessment is based on older studies. Jessica added that the portal-of-entry effects and the 2012 guidance has a huge effect; it causes the point of departure to go down to one tenth of the value using the previous guidelines versus the default factor of 1:1 that is recommended now. Jessica said that even though the 2012 guidance document came from EPA, most of EPA still refers to the older guidance and ATSDR does not use the new inhalation guidance. Jessica reiterated that Oregon's policy should guide the value selection because that will determine which sources' values make the most sense. John Stanek shared that the 2012 EPA document being referenced is a status report that is being adopted by some but is not official guidance. Daisy shared that at CalEPA, they adopted the conversion factor of one for port-of-entry effects from the newer guidance. Jessica shared that TCEQ also adopted the updated inhalation reference and retroactively updated values that were based on the old guidance.

#### Acute TRVs

| Order of Preference | Agency Name    | Name of Acute TRV | Assumed Exposure Time                 |
|---------------------|----------------|-------------------|---------------------------------------|
| 1                   | U.S. ATSDR     | Acute MRLs        | Less than 2 weeks (includes 24 hours) |
| 2                   | California EPA | Acute RELs        | 1 Hour                                |
| 3                   | U.S. ATSDR     | Intermediate MRLs | 2 weeks to 1 year                     |

Next, Holly showed a table that includes the authoritative sources, acute TRV names, and assumed exposure times. As mentioned earlier, DEQ and OHA assume 24 hours of exposure for acute TRVs. Holly noted that in terms of acute TRV application, the Cleaner Air Oregon program is not intended to be a mechanism to address emergency situations where exposures of less than an hour could affect health. There are mechanisms to address emergency situations other than how these values will be applied.

In the past, DEQ and OHA chose acute TRVs from the authoritative sources with exposure times that best matched DEQ and OHA's assumed exposure time of 24 hours. This table shows the authoritative sources listed in order of that preference. DEQ in consultation with ATSAC can also set an acute TRV. This provides flexibility in choosing and setting acute TRVs that best match the 24-hour exposure duration definition. Holly pointed out that there are some existing acute TRVs that are derived from, or are equivalent to, chronic values. This has occurred in two different types of situations. The first is when it is not clear when developmental health effects are initiated within the developmental period. The second is when the acute TRV chosen is a lower value than the chronic TRV. In these cases, we set the acute TRV to be equal to the chronic TRV. Holly acknowledged that deriving acute TRVs from chronic TRVs is not ideal and, where appropriate and possible, DEQ and OHA would prefer to derive an acute TRV from a study with an acute exposure duration. During their review of acute TRVs, the agencies plan to try to find alternative TRVs that are based on studies with short-term/acute exposure periods. Holly noted that the project team is interested in any feedback from ATSAC members on how to best look for



acute TRVs from other organizations and have an order of preference to help select TRVs to bring to the committee in future meetings to discuss.

**Discussion Questions: Do you have questions or feedback on the authoritative source order preference for selecting acute TRVs?**

**Can you recommend other sources of acute TRVs the agencies should consider while prioritizing review of toxic air contaminants where the current acute TRV is equal to the chronic non-cancer TRV or based on chronic studies?**

- Jefferson Fowles: Jeff shared that he does not have any major disagreements with the authoritative source order as listed. The use of the OEHHA acute one hour exposure value will present some extrapolation issues to go to 24-hour exposure, especially for some chemicals. For chemicals that are almost entirely portal-of-entry concerns, it may not be as big of an issue. If the issues related to extrapolation are caveated appropriately, this should be okay. It will also likely require the use of an uncertainty factor. In terms of additional sources of acute values, it might be useful to investigate acute reference doses that exist by agencies that collect or require that information from companies that conduct studies to meet regulatory requirements. For food safety, there are acute reference dose lists from sources such as WHO and the European Food Safety Authority. Those could be areas where the group could consider drawing upon at least the key studies if a chemical has a systemic effect. For acute reference doses, it's typically not done for inhalation exposures, so you must take the systemic effect and reach a conclusion, whether or not it can be easily translated to an inhalation scenario. The European Food Safety Authority and other country authorities like Australia that derive or require companies to provide data that they derive the values from. There are various ways that agencies end up with these numbers, but at least it does provide an acute number. These are often based on animal studies that are not necessarily an acute exposure, they may be a developmental or reproductive toxicity study. There could be a subacute study. It's very rare to find a one-hour exposure studies. Typical acute studies used for classification and labeling are not going to be sensitive enough to pick up subtle effects. There might be some utility in looking at an assembly of acute reference doses that exist internationally.
- John Vandenberg: John suggested that language should be added to the issue brief to clarify that the toxicity reference values being discussed are for acute exposures, not for acute effects. There can be long-term effects from acute exposure, like developmental toxicity. This group probably understands that the acute TRVs refer to exposure, but this should be clear and explicit to avoid confusion for the reader. John also noted that it would be more helpful if the table of chronic TRV values was separated by cancer and noncancer values. John advised that the project team be as clear as possible in distinguishing exposure versus effects when discussing acute or chronic exposures and either cancer or noncancer effects. There are studies that have been done of just a couple of hours of exposures, particularly for developmental and neurological effects, that can have lifelong effects.
- John Stanek: John shared that the majority of sources he can think of, such as the EPA's Acute Exposure Guideline Levels (AEGL) values, were based on acute values for inhalation associated with advisory levels and emergency situations.

- Jefferson: Jeff agrees that the AEGL values do not have margins of safety built in that a lot of other values do. However, they often have a fairly rigorous assessment of the time duration adjustment. That could be potentially useful to try to assess to what degree a study of a different duration the TRV needs. It might be useful to consider some of these documents even if the numbers themselves are not perfect fits.
- John Budroe: The AEGLs might be useful as a secondary source, but the numbers tend not to be that useful for this context. John shared that extrapolating from AEGLs for acute health values is something that OEHHA would only do with great trepidation and did not ultimately do.
- Daisy: DPR had the same problem with reference doses. Their strategy, since they are equipped with resources for comprehensive risk assessment, is to look through all the studies for any short-term or acute effects. Even in a chronic study, it's sometimes possible to find an endpoint that represents an acute exposure effect. For Oregon, the best approach might be if there's no acute TRV, to look at to the development studies. DPR assumed a developmental window exposure that could have resulted from a one-day exposure. It's a reasonable assumption that the effect could be derived from a single day. ATSDR has a toxicological profile, and the agencies could look at their developmental studies to see if there's any effect that they can use to derive acute exposure. Another alternative is to use any short-term study, such as within a week of exposure. Using a chronic value is the last option. DPR has a tiered process. For full risk assessment, they look at any study to find any effect associated with acute exposure.
- Jessica Myers: TCEQ has acute values for all the chemicals that are monitored in the state of Texas. Whether those have gone through a full review or have used surrogation or read across to develop them, those are available. Jessica also shared that she would hesitate to use ATSDR intermediate values to derive an acute value considering that some of those studies could be based on exposures up to a year and Oregon is trying to develop a value for a single day. That kind of duration adjustment might not be practical.

Holly asked if the group if the Superfund Health Risk Technical Support Center (STSC) is a source within EPA that DEQ and OHA should be looking into. ATSAC members were not familiar with this program.

## TRV Workflow Presentation

Holly outlined the proposed TRV review process. After considering all the feedback heard from ATSAC members during this meeting, DEQ and OHA will begin the next steps of this TRV review process. DEQ and OHA will have two sets of TRVs to review. The first is the list of existing TRVs. These are currently in rule, and the project team wants to check this list to see if there are any updates and make sure all the information is accurate. Then, they will also check for any updates to the list of priority toxic air contaminants to see if any new TRVs should be added. For the sets of TRVs to review, agency staff will check TRV information from all authoritative sources and gather information on other TRVs that could be adopted from other organizations or developed. Gathering information from other organizations will be dependent on the factors discussed today as well as staff bandwidth.

Then, agency staff will select initial TRVs using the processes discussed today. Agency staff will hold a series of meetings with ATSAC to share a variety of information learned during the review and ask for feedback. During these meetings, agency staff will share the results of the TRV selection process and ask ATSAC members technical questions that arose during the review process. They expect to discuss other

tangential work and decisions during those meetings. One example of other tangential work are the hazard index designations. In future meetings, DEQ and OHA may consult with the ATSAC about whether a toxic air contaminant meets the criteria in rule for changing hazard index designations. In follow-up ATSAC meetings, DEQ and OHA will seek input from the ATSAC if they propose to deviate from the predetermined process or propose to use a TRV that is not from one of the three main authoritative sources.

Currently, the project team anticipates consulting ATSAC members on TRVs for at least two air contaminants, including manganese (acute TRV) and diesel particulate matter (chronic cancer TRV). The agencies expect to add to and update this list while proceeding with the TRV review process and will share those updates with ATSAC.

Holly also provided an overview of the TRV Update Tool that DEQ and OHA have developed and are continuing to refine to organize the review of existing TRVs and to add new TRVs to the list. This tool is an organized excel spreadsheet for aggregating and reviewing authoritative source information. While the project team is not seeking feedback on the layout or setup, they wanted the ATSAC members to be aware of the tool they are developing and how they plan to use it.

The tool is designed to work on one chemical at a time to reduce the chance of entering data for the wrong chemical. Agency staff will enter in information from each authoritative source for each contaminant with at least one TRV. This tool is more than a data entry form; it also aggregates information and allows side-by-side comparison to visually confirm changes and has built-in checks to minimize entry errors. The agencies will also use the tool to track decision-making. For example, when the project team proposes to deviate from the normal algorithm, the rationale can be recorded within the tool. Further, the tool also creates comprehensive key tables of all the information that is entered. These key tables can be queried in any number of ways and the proposed changes are all trackable and directly linked to the appropriate reference information.

The team designed this tool with future iterations of this review in mind. The end goal is to turn this tool into a database for the next round of TRV review. They are investing a lot of time in the development of this tool since they intend to use it to streamline review, minimize input error, and track changes across future TRV update cycles.

Holly also pointed out that reviewing TRVs will be a large, time-consuming effort for their team. They expect that data entry, decision making in the tool, and quality control processes will take hundreds of hours of staff time. The work is expected to be this time-consuming for several reasons, including that they need to look for new TRVs that are not currently in rule; they need to check for new data and sources of information about TRVs they already have; and they want to verify the units, dates, and other information of each TRV as they transition to this new TRV tool. They also need to track target organ information, which is not present in most lists from authoritative sources, and they need to track additional information related to hazard index designations.

**Discussion Questions: Do you have questions or comments on the proposed process for reviewing and providing feedback on DEQ's and OHA's work?**

**What other feedback or input do you have for DEQ and OHA?**

- John Vandenberg: Is this tool or the results going to be publicly available?
  - Holly: They are trying to figure out what version to make public. The entire tool is public record, but they were thinking about making some of the summary tables accessible and available online. The database is the end goal.
  - John shared that considering the work and time that is being put in, this tool would be valuable for other organizations to benefit from this work.
  - It could be possible to export the tool into a format that people can search and sort independently.
  - Kristen Martin, DEQ, added that the structure of the tool is that it is capturing this data in background tables that can be summarized in many ways. The team has been brainstorming different ways to make these tables.
  - John added that if they can create an export function, that would be very helpful for users.
  - John Budroe: John agreed that it would be beneficial to be able to export this tool and allow people to use it.
- Daisy: Daisy added the challenge will come when there are multiple values from different authoritative sources: If there's more than one value, how do you choose? Each agency has their own guidance and methods, so it will eventually come down to Oregon's own hazard risk assessment decision.
- Holly provided some additional details on how the tool is built. There is a tab for each chemical and a section for each authoritative source, and then there is another section for DEQ. They have flexibility and can add additional criteria here. There's also a summary table at the end that summarizes all the information so they can visually compare it and make a selection. Holly shared that they are also deciding how much information to put in the tool and how much time to spend on each individual source.
  - Kristen added that the tool will show a recommended value based on the embedded logic, and the team can choose to use that recommended value or not.
- Daisy: Do you attach the critical study and justification in the table, or just put the values?
  - Holly: Right now, the tool tracks the value, the date the value was created, and who it was created by. There's also a separate place with target organ information for each chemical that tracks the critical effect, a link to the documentation, uncertainty factors, and any information on developmental or reproductive hazards. They are tracking this information and there is flexibility to change this at this time.

David asked if any ATSAC members know the locations of comprehensive lists of all the reference values that their organization has, that would be helpful to send to the project team, especially if there are particularly useful lists that include a lot of data in one place. David shared that the team already has this information for IRIS, PPRTVs, and ATSDR, but may not have this for OEHHHA. These kinds of lists are helpful for populating the tool with data.

- John Budroe said that he can check if he has access to a similar list from OEHHHA that he can share.
- John Vandenberg added that for some systems like IRIS and PPRTVs, there's a public-facing component, but the team may be able to contact the staff and they may be able to have the

programmers export the data, which would facilitate uploading that data into Oregon's system and save the team some time.

- Jessica shared that TCEQ moved to a database system, and they are able to create Excel files from that system. They can also specify which types of chemicals are exported.

Ben asked if any ATSAC members have final questions or comments. ATSAC members shared that they agree with Oregon's approach and commended the team for the work done so far.

- John Vandenberg: Air toxics can be challenging due to limited availability of scientific information and studies. There are a certain number of chemicals that are always of concern to the public. There might be other sources of potential exposure information, such as the toxic waste inventory and pesticides registration, that might be appropriate to consider. In North Carolina, they are monitoring the level of exposure to emerging contaminants such as PFAS and PFOA chemicals. As Oregon develops their list of chemicals, they might want to consider emerging contaminants that have not been recognized in the past.
- John Budroe: There are other sections in OEHHA that are also working on pulling in values from other state and federal programs. For example, there is a program at CalEPA called the Study of Neighborhood Air near Petroleum Sources (SNAPS) that looks at emissions from oil and gas facilities. It might be possible to share information with people working on this program that are encountering similar challenges.
- John Stanek: John shared that in the appendices of the report that he shared with the project team, there are references to a couple databases that have since moved. John will try to locate and share these databases that DEQ can potentially use as another resource.

## Closing and Next Steps

Ben asked the project team to share the next steps. Matt noted that the first step is for the project team to debrief what was discussed during this meeting and invited ATSAC members to send any additional thoughts after the meeting to the team via email or an offline conversation for the next couple of weeks following the meeting. David added that the meeting minutes are the main deliverable and public record from ATSAC meetings, and the ATSAC members will have an opportunity to review the meeting minutes to ensure that comments were captured accurately.

Matt shared that the project team will finalize the logic that will be embedded in the tool and will communicate this decision to the ATSAC. DEQ and OHA will come back to the ATSAC and share the results of this initial screening. That will also give the team a better sense of the overall workload and how many chemicals they anticipate investigating throughout this review process. Over the next couple months, the team will work through the process to bring a specific list of chemicals to the ATSAC. The next ATSAC meeting will likely not be for several months. Ben thanked everyone for participating and adjourned the meeting.

## Summary of Resources Recommended by ATSAC Members

- Appendix G in the U.S. EPA 2016 report titled ["Hydraulic Fracking for Oil and Gas: Impacts from the Hydraulic Fracturing Water Cycle on Drinking Water Resources in the United States"](#)

- U.S. EPA 2012 report titled “[Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration \(RfC\) and Use in Risk Assessment](#)”
- [U.S. EPA CompTox Dashboard](#)
- North Carolina Environmental Quality Secretaries’ Science Advisory Board October 2022 Presentation (available upon request)

# **Appendix C: Meeting Minutes for ATSAC Meeting #3 on the Manganese Petition**

# Air Toxics Science Advisory Committee (ATSAC) Meeting 3 Minutes

April 3, 2024 12:00-2:30 pm PT

The third meeting of the Air Toxics Science Advisory Committee



## Meeting Minutes

### Meeting Attendees

| ATSAC Members           |                                                      |
|-------------------------|------------------------------------------------------|
| Jefferson (Jeff) Fowles | New Zealand Food Safety                              |
| John Budroe             | California Environmental Protection Agency (retired) |
| John Stanek             | Environmental Protection Agency (EPA)                |
| John Vandenberg         | Duke University                                      |
| Qiaoxiang (Daisy) Dong  | California Environmental Protection Agency           |
| Susan Tilton            | Oregon State University                              |
| Project Team            |                                                      |
| Ali Mirzakhilili        | Oregon Department of Environmental Quality (DEQ)     |
| Apollonia Goeckner      | Oregon Department of Environmental Quality (DEQ)     |
| David Farrer            | Oregon Health Authority (OHA)                        |
| Holly Dixon             | Oregon Health Authority (OHA)                        |
| J. R. Giska             | Oregon Department of Environmental Quality (DEQ)     |
| Kristen Martin          | Oregon Department of Environmental Quality (DEQ)     |
| Molly Notarianni        | Oregon Health Authority (OHA)                        |
| Susan MacMillan         | Oregon Department of Environmental Quality (DEQ)     |
| Facilitation Team       |                                                      |
| Ben Duncan              | Kearns & West                                        |
| Bianca Valdez           | Kearns & West                                        |

Meeting slides can be found at <https://www.oregon.gov/deq/aq/Documents/ATSACM3slides.pdf>

## Welcome and Introductions

J. R. Giska, Oregon Department of Environmental Quality (DEQ), opened the third meeting of the Air Toxics Science Advisory Committee (ATSAC) and outlined its purpose: to provide expertise for revising Air Quality Standards, specifically Toxicity Reference Values (TRVs), which regulate industrial emissions of Toxic Air Contaminants. He emphasized that the committee, reinstated in

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2021, collaborates with Oregon DEQ and Oregon Health Authority (OHA) in this effort. The meeting focused on a petition concerning the acute, or 24-hour, TRV for manganese. He explained that the petitioners would share scientific materials, followed by a guided discussion among the ATSAC members to inform potential updates to the acute manganese TRV by DEQ and OHA. The ATSAC comprises volunteer toxicology professionals and does not make policy decisions, and the meeting would therefore focus on scientific discussion regarding the petition, excluding policy or fiscal considerations. J.R. thanked the petitioners and ATSAC members for joining and introduced DEQ's AQ Program Administrator, Ali Mirzakhali.

**Ali Mirzakhali, DEQ**, thanked members for attending the meeting to inform DEQ's Cleaner Air Oregon program. He explained the program provides the AQ permitting program with the tools to ensure that DEQ can issue permits that meet health-based standards. Central to this important goal is making sure that DEQ maintains its standards, including the TRVs, based on the most up-to-date science. Ali expressed gratitude for the member's expertise and support and thanked the petitioners for engaging DEQ on this issue.

**David Farrer, OHA**, welcomed the members and highlighted the strong partnership between OHA and DEQ since the program's inception.

**Ben Duncan, Kearns & West (K&W) facilitator**, reviewed the Zoom webinar protocols, facilitated introductions from the DEQ and OHA project team, and conducted a roll call of ATSAC members. Ben reviewed the meeting agenda, which included 1) Welcome, 2) Updates on TRV Review, 3) Petitioner Manganese Presentation, 4) Review Tables in Manganese Framing Document, 5) Discussion of Key Questions and 6) Closing and Next Steps.

## Updates on TRV Review

**Holly Dixon, OHA**, provided TRV review updates (slides 4–10). She reminded members of the previous discussion on the TRV review process in earlier ATSAC meetings, seeking feedback on a proposed method for selecting TRVs from multiple sources for acute and chronic exposure. She listed authoritative sources of toxicity information known for their scientific rigor and comprehensive methods, which DEQ considers in setting and updating TRVs. These sources are listed in the Oregon Administrative Rules and were adopted by DEQ's Environmental Quality Commission.

In 2021, the Environmental Quality Commission designated Oregon DEQ, in consultation with ATSAC, as an authoritative source. This grants DEQ and ATSAC greater flexibility in updating TRVs, allowing DEQ, in consultation with ATSAC, to develop TRVs and consider TRVs from entities in addition to the U.S. EPA, U.S. ATSDR (Agency for Toxic Substances and Disease Registry), and CalEPA.

She discussed DEQ's development of the TRV Update Tool, which streamlines the review of existing and newly added TRVs. Over the past year, DEQ has spent considerable time refining this organized Excel spreadsheet, which aggregates and reviews authoritative source information. The tool is designed in a way that allows the user to work on one chemical at a time to reduce the chance of entering data for the wrong chemical. Holly explained how they entered information from each authoritative source for each contaminant with at least one existing or potentially new TRV. She

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emphasized how the tool is more than a data entry form, as it allows the user to aggregate information and have a side-by-side comparison to visually confirm changes. DEQ and OHA have completed the data entry and initial TRV decision-making in the tool for all toxic air contaminants that either had existing TRVs in Oregon Administrative Rule or that could potentially have new TRVs. Holly then provided brief updates on their overall progress over the past year. OHA and DEQ carefully considered feedback from the previous ATSAC meeting and subsequently modified both the process and the TRV Update Tool. A summary of changes can be found in the *Proposed TRV Update and Selection Process for ATSAC Review* [document](#). As mentioned previously, the team finished a full initial review of existing and new TRVs. The team reviewed at least four authoritative sources of TRV information by hand for about 1,200 potential TRVs for 400 toxic air contaminants. They reviewed and recorded information on TRV values, critical studies (including information such as date of study, author, and point of departure method used), uncertainty factors, developmental and reproductive hazards, and more. Beginning in early 2024, DEQ and OHA contracted with the Eastern Research Group (ERG) to verify the information recorded by the authoritative sources within the TRV tool. ERG has provided technical support for multiple environmental and health agencies (such as the U.S. EPA and ATSDR) for more than three decades. Holly explained they will share the results of the TRV review with the ATSAC, and all the information shared will have gone through the quality control process. When this quality control process is complete, DEQ and OHA will put together materials for the members to review and conduct a series of ATSAC meetings to discuss the proposals for the TRV updates.

Holly then introduced the petitions for TRV changes. As part of the TRV review process, DEQ Oregon Administrative Rules permit members of the public to submit petitions proposing TRV updates. DEQ welcomed petitions for consideration during the current TRV update process. Petitions were due in late 2022, and DEQ received one petition to change DEQ's TRV for acute exposure (24-hour) to manganese (hereafter referred to as the "acute TRV"). This petition was prepared by Bridgewater Group, a consulting firm that works extensively with sources in Oregon on air quality permitting actions, including Cleaner Air Oregon risk assessments. The toxicological information and analysis for the petition were provided by ToxStrategies, a scientific consulting firm. The petition proposes to increase the DEQ acute manganese TRV from 0.3 µg/m<sup>3</sup> (micrograms per cubic meter) to 5 µg/m<sup>3</sup>. The 5 µg/m<sup>3</sup> is consistent with the 24-hour ambient monitoring comparison value developed by the Texas Commission of Environmental Quality (TCEQ). While the TRV proposed in the petition is equivalent to the TCEQ TRV, the petition proposes a slightly different set of uncertainty factors (UFs) than the ones used by TCEQ, which are discussed in detail in the framing document.<sup>21</sup> Staff at ToxStrategies also published a peer-reviewed manuscript in 2023 on this acute TRV development ("Perry et al."). The manganese acute TRV proposed by Perry et al. is also equivalent to the TCEQ TRV and petition TRV. However, Perry et al. propose a slightly different set of UF's than the ones used by TCEQ and by the petitioner, which are discussed in detail in the framing document. Holly concluded by explaining members would now receive a presentation on the petition from ToxStrategies, with DEQ and OHA looking forward to ATSAC's feedback on the matter.

## Petitioner Manganese Presentation

**Ben, K&W facilitator**, introduced ToxStrategies presenters Ann Verwiell and Camarie Perry, and Travis Quarles from Bridgewater Group. Ben explained in the fall of 2022, as part of the TRV Review and Rulemaking, DEQ solicited petitions from the public to add or remove chemicals from the Priority

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List of chemicals, to remove a chemical from the TRV list, or to revise or add a TRV. The Bridgewater Group submitted a petition to change the acute value of manganese, and the information included in that petition was prepared by Tox Strategies, who will be talking to ATSAC about their methodology. Ben explained the petitioners would have a half hour to present and members to participate in a question-and-answer session. Ben encouraged ATSAC to ask questions about the Petitioner's proposals for UFs.

**Travis Quarles, Bridgewater Group**, opened the presentation by thanking staff and ATSAC members for their time and for the opportunity to present the petition.

**Camarie Perry, ToxStrategies**, presented on the *Derivation of Manganese 24-hour Acute Inhalation Guideline*[\[3\]](#) (slides 12-31). As opposed to most other regulated compounds, Camarie noted that manganese is unique, as it's an essential nutrient and is necessary for the proper functioning of the body. It has a U-shaped dose-response curve, therefore, too little or too much of this nutrient is problematic and levels in the body need to be kept in the middle of the range. ToxStrategies stated that an air level of 5 µg/m<sup>3</sup> would not increase a person's internal stores of manganese. This proposed level would be health-protective for years of exposure. DEQ's preference is that acute guidelines be developed from acute toxicity studies; therefore, ToxStrategies', short-term value is based on short-term studies.

Camarie further introduced herself and her background, highlighting her experience as a state regulator for the Texas Commission of Environmental Quality (TCEQ) and a consultant. She also introduced her colleague Ann Holbrow Veriweil who has over 20 years of experience in environmental risk assessment consulting. Both Camarie and Ann have extensive experience in human health risk assessment, evaluation of air emissions, developing remediation guidance, exposure and toxicity evaluations, and metals.

Camarie presented on general manganese toxicity, reiterating that it is an essential element that is beneficial at low concentrations and its absorption and excretion are controlled by homeostasis. Manganese is critical for neurodevelopment and exhibits an inverted U-shaped dose-response curve. During development, both manganese deficiency and excess can result in neurocognitive effects. Through homeostasis, systemic background levels are in the optimal range for health. Since manganese toxicokinetics are non-linear, derivation of toxicity criteria has been challenging as standardized UFs are not always applicable. Neurological effects are the most sensitive endpoints for chronic exposures, but respiratory effects can occur with acute exposures.

She shared that ToxStrategies' objective was to develop a 24-hour acute health guideline value protective of respiratory and neurological effects and use current physiologically based pharmacokinetic (PBPK) models to address potential manganese accumulation in critical brain compartments such as the globus pallidus during sensitive developmental life stages. They derived an acute, 24-hour guideline for manganese inhalation exposure of 5 µg/m<sup>3</sup> based on 3-week (90-hour) monkey studies evaluating respiratory effects (Dorman et al. 2005) as well as oxidative stress markers in the brain (Erikson et al. 2008). She noted the group would discuss UFs in more detail later. The PBPK modeling was used to confirm that 5 µg/m<sup>3</sup> acute exposures do not significantly increase manganese in brain tissues (e.g., globus pallidus – primary target tissue for manganese accumulation & neurotoxicity).

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She provided further information on the PBPK modeling. PBPK models predict manganese accumulation in sensitive brain compartments, including the globus pallidus, from oral and inhalation exposures, and for multiple life stages. PBPK models are particularly useful for manganese to address the challenges of assessing manganese accumulation considering homeostasis and potential neurotoxicity (Yoon et al. 2019; Campbell et al. 2023). From Yoon et al. (2011 and 2019), ToxStrategies used the “lactation/infant” and the “child/adolescent/adult” model codes, respectively. ToxStrategies focused on the child/adolescent/adult model code because it predicted higher globus pallidus concentrations. They evaluated potential outcomes for two short-term exposure scenarios at 5 µg/m<sup>3</sup> manganese.

1. Monthly exposure scenario: A 24-hour inhalation exposure one time per month, from birth throughout life, with diet and ambient air exposures set to background levels.
2. 3-Week exposure scenario: A single, 3-week period of constant inhalation exposure at age 3, since the model predicts the highest manganese levels in globus pallidus at ~3 years of age, with diet and ambient air exposures set to background levels. (*Scenario with highest tissue manganese accumulation.*)

Camarie presented the PBPK modeling results (slide 17) with a figure from the Perry et al. 2023 publication. The figure displayed the highest concentration from the 3-week exposure scenario from males aged 3-5 with the highest manganese concentrations in the globus pallidus. The highest background concentration was 0.535 µg/g, and the highest modeled concentration was 0.552 µg/g, which was 3 percent above background in the globus pallidus. Therefore, neither exposure duration (24-hour exposure monthly or 3-week continuous exposure) results in manganese concentrations significantly above background exposures. The predicted manganese levels in the globus pallidus are lower than the tissue-based no-observed-adverse-effect levels (NOAELs) for neurotoxic effects in humans and monkeys which range from 0.7-0.9 µg/g (Gentry et al. 2017, Schroeter et al. 2012). Therefore, an acute TRV of 5 µg/m<sup>3</sup> even with 3 weeks of continuous exposure would not result in significant exposures above background or NOAELs in humans and monkeys. She also presented a bar graph of the predicted manganese tissue concentration in 3 to 10-year-olds (µg/g). Multiple brain tissues and whole blood and liver tissue concentrations of manganese were not above background under either exposure scenario.

Next, she referenced DEQ’s framing document, which summarizes information relevant to the proposed manganese acute TRV. She highlighted the following from the document:

“DEQ acknowledges that deriving **acute TRVs from chronic TRVs is not ideal** and, where appropriate and possible, DEQ would prefer to derive an acute TRV from a study with an acute exposure duration.”

“DEQ agrees that TCEQ’s manganese acute TRV is a good resource because:

1. TCEQ’s acute TRVs match DEQ’s acute exposure time (24 hours),
2. TCEQ’s manganese acute TRV is based on short-term toxicity study data, and
3. TCEQ provides comprehensive developmental support documentation.”

Camarie then discussed the uncertainty factors, or UFs, used. Individual UFs are not completely independent of each other. This is especially true for essential nutrients which display a U-shaped dose-response curve and combining default UFs of 10 can lead to double-counting. Therefore, EPA, OEHHA, and TCEQ have developed upper limits on total UFs for inhalation guidelines. For example, both EPA (2002) and OEHHA (2008) limit total UFs for chronic inhalation exposures to 3,000.

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Similarly, TCEQ limits total UFs for acute inhalation guidelines to 300. As ToxStrategies' understanding of the issues has expanded over time, they're recommending the same guideline of 5 µg/m³, but slightly different UFs between the petition and the publication (Perry et al. 2023). There are various UFs for determining proposed acute guidelines for manganese. Camarie presented the UF options across the various entities. The chart presented values from ODEQ's proposed range of potential options, TCEQ's (2017) 24-hour guideline, ToxStrategies' support for Petition to ODEQ (Nov. 1, 2022), and the proposed 24-hour Acute Guideline for manganese (Perry et al. 2023). She noted they assumed a mild lowest-observed-adverse effect level (LOAEL) of 1.5 mg/m³ and then reviewed UF options. The colored columns in the chart (slide 21) indicate three individual UFs (i.e., UF<sub>A</sub>, UF<sub>L</sub>, and UF<sub>D</sub>) that differ between the various entities.

Camarie then reviewed the three different UFs, reviewing the recommended value and rationale for each. Below is a table with this information:

| Uncertainty Factor                                                       | Recommended Value | Rationale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interspecies (UF <sub>A</sub> )<br>Range in Framework Document: 3 - 10   | 3                 | <p>A UF<sub>A</sub> of 3 was used since monkeys largely replicate the toxicodynamic neurobehavioral effects of Mn observed in humans (Schroeter et al. 2011; Gentry et al. 2017) (UF<sub>A-D</sub> of 3), and toxicokinetics between monkeys and humans in the Dorman et al. (2005) and Erikson et al. (2008) studies are essentially equivalent (UF<sub>A-K</sub> of 1).</p> <p>PBPK modeling was used as an additional line of evidence supporting consistent toxicokinetics between monkeys and humans.</p>                                                                                                                                                 |
| LOAEL to NOAEL (UF <sub>L</sub> )<br>Range in Framework Document: 2 - 10 | 10                | <p>Although effects were mild, a UF<sub>L</sub> of 10 was used for conservatism and protectiveness, and since PBPK modeling showed tissue Mn levels did not immediately return to background levels following cessation of the 3-week continuous exposure (returned to background in &lt;6 months).</p> <p>This is a conservative assumption, since the respiratory effects were mild, and no clinical effects were observed in monkeys in the Dorman et al. (2005) and Erikson et al. (2008) studies and the lack of data for a continuous 24-h exposure period.</p> <p>Due to the study designs of Dorman et al. (2005) and Erikson et al. (2008), post-</p> |

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|---------------------------------------------------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                     |   | exposure recovery data are not presented for the 90-hour exposure group.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Database (U <sub>D</sub> )<br>Range in Framework<br>Document: 1 - 6 | 1 | <p>General Considerations:<br/>Database insufficiency factor – “Adjusts for the possibility of identifying a lower (or more sensitive effect) if additional studies were available” (Dankovic et al. 2015).</p> <p>In determining UF<sub>D</sub> - Evaluate the specific kinds of available data and weigh the likelihood that additional studies would reveal more sensitive toxicity/endpoints.</p> <p>A UF<sub>D</sub> of 1 was used because it is considered unnecessary to impose a UF<sub>D</sub> factor for reproductive or developmental effects.</p> <p>In a rat developmental drinking water study with Mn up to 4 mg/L, Oshiro et al. (2022) reported no cognitive impairment among offspring when combined with maternal stress.</p> <p>Epidemiologic studies in children have shown cognitive effects in children associated with elevated blood manganese, but the range of blood Mn levels associated with cognitive effects varies considerably (Bhang et al., 2013; Haynes et al., 2015). Blood Mn levels in the PBPK model were consistent.</p> <p>Similarly, Chung et al. (2015) observed neurocognitive deficits among the offspring of mothers with low and high blood manganese relevant to the U-shaped dose-response curve.</p> <p>Although this uncertainty is not specifically accounted for, an additional uncertainty factor is not likely necessary because the PBPK modeling demonstrates that tissue Mn levels (blood, liver and brain including the globus pallidus) are not affected</p> |

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|  |  |                                                                    |
|--|--|--------------------------------------------------------------------|
|  |  | significantly at 24-hour exposures of 5 $\mu\text{g}/\text{m}^3$ . |
|--|--|--------------------------------------------------------------------|

Camarie explained their proposed acute guideline of 5  $\mu\text{g}/\text{m}^3$  is low compared to published chronic inhalation values from the following literature:

- Bailey et al. (2009) proposed 2  $\mu\text{g}/\text{m}^3$  to 7  $\mu\text{g}/\text{m}^3$  as chronic reference concentrations.
- Schroeter et al. (2011) and Gentry et al. (2017) predicted that homeostasis maintains manganese levels in the brain target tissue at airborne concentrations below 10  $\mu\text{g}/\text{m}^3$ .
- Yoon et al. (2011) indicates that maternal and fetal blood manganese levels are not affected at airborne concentrations less than 10  $\mu\text{g}/\text{m}^3$ .

In summary, Camarie concluded that by using PBPK methods, this study supports a 24-hour acute guideline for environmental exposures of 5  $\mu\text{g}/\text{m}^3$ , which is equal to the value set by the TCEQ. Essential nutrients have unique pharmacological and toxicological properties and therefore require alternative considerations in setting guideline levels and consideration of background tissue concentrations that are beneficial. The PBPK modeling demonstrates that the guideline is protective of both respiratory and neurological effects, as manganese is not expected to accumulate in key tissues. ToxStrategies recommended a combined UF of 300 applied to the point of departure (POD) of 1.5  $\text{mg}/\text{m}^3$ , based on the following individual UFs:

- $\text{UF}_A$ : 3 for similarities in neurobehavioral effects and toxicokinetics between monkeys in humans
- $\text{UF}_H$ : 10 for sensitive human subpopulations (conservative due to PBPK modeling for sensitive life stages.)
- $\text{UF}_L$ : 10 for mild LOAEL to NOAEL (conservative)
- $\text{UF}_S$ : 1 since key study was 90 hours (longer than target of 24 hours)
- $\text{UF}_D$ : 1 since manganese is an essential nutrient and necessary for development. PBPK modeling indicates that the proposed 24-hour guideline of 5  $\mu\text{g}/\text{m}^3$  is not expected to significantly increase critical brain compartment, blood and other tissue compartments over background or NOAELs; and the guideline is low compared to chronic thresholds.

Ben thanked ToxStrategies for presenting and opened the meeting for discussion. He reminded the members that the petitioners would be available for the remainder of the meeting.

Below is the question-and-answer session that followed:

- **John Vandenberg** inquired about ToxStrategies reasoning for selecting an exposure occurring once per month throughout life (monthly exposure scenario) throughout life for the PBPK model.
  - **Camarie Perry** explained that a monthly exposure scenario was what they felt would be appropriate to align with the 24-hour regulatory guideline concentration, representing a reasonable level of exposure. Additionally, the existing acute TRV was derived from data spanning five years of exposure. ToxStrategies also incorporated a three-week continuous exposure scenario to address the timeframe considered by ODEQ, ensuring a conservative approach.
  - **Ann Holbrow Veriweil** agreed and noted that, from a regulatory standpoint, if a facility occasionally exceeds acute guidelines once a month, it raises questions about the operational status. Similarly, being consistently at the acute guideline level for an extended period, such as a few weeks, prompts considerations of compliance with the chronic TRV. Acute guidelines are intended for short-term, unusual situations.

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- **John V.** asked if the six-month period until levels returned to background occurred after the three-week or 24-hour exposure.
  - **Ann V.** clarified it was after three weeks, and the focus of today's presentation was on the worst-case scenario in the PBPK modeling.
- **John V.** noted discontinuity around 3.25-3.5 years of age, where model concentrations abruptly increased. He inquired on the cause of this occurrence.
  - **Ann V.** explained the person most familiar with the model is not available, however, she would reach out to them with this question.
  - **Jeff Fowles** noted it might have to do with infancy or early childhood breastmilk exposure.
  - **Ann V.** responded that the graph depicts a three-week exposure for a 3-year-old child, so that is not considered a potential exposure at that point in time.
- **Jeff F.** asked about the selection of background or dietary levels of manganese in the primate's diets. He inquired if the background levels in the modeling explored the upper limits of what would be considered normal in a typical human diet.
  - **Ann V.** explained the background levels in the modeling are based on levels used by PBPK modelers who wrote the papers. Regarding the comparison to background levels in the studies from which the point of departure was derived, ToxStrategies did not make that comparison directly but relied on modelers to provide them with typical ambient background exposures.
  - **Jeff F.** acknowledged that the conclusions would remain the same even if the background is higher.
- **John Budroe** added a clarification to a ToxStrategies slide that referenced other agencies having cumulative uncertainty factors and the issue of double counting. John B. stated that he knows that OEHHHA (and thinks that IRIS is similar) does not have a cap on cumulative uncertainty factors. Instead, if a cumulative uncertainty factor becomes larger than 3,000, then the data set is considered to be too uncertain to derive a TRV, either chronic or acute. Overall, it's not an uncertainty factor interactivity concern and it's not an uncertainty factor cap, it's more that OEHHHA uses the total uncertainty factor to decide whether or not to use the dataset.
- **Daisy Dong** noted that two studies in the petition (Erikson et al. 2005 and 2006) involve in utero exposure. She asked if ToxStrategies looked further into those studies and others (including rat studies) for more information on in utero exposures and endpoints. For manganese, the neurological effect is clearly related to oxidative stress, so did ToxStrategies look into any of those gene expression reports?
  - **Camarie P.** explained that rat studies may not be as applicable to humans as studies involving monkeys. There's less emphasis on rat studies to replicate human neurotoxic effects, especially concerning breathing given toxicokinetic differences. Each species reacts differently, so if they pursued rat studies, they would focus on in utero exposure and potential developmental effects.
  - **Daisy D.** responded that the monkey study only provides a single dose, which is a limitation of the critical studies, and noted it would be good to see some endpoint related to *in utero* exposure perhaps in rodents.
- **Daisy D.** asked why there was no exposure time adjustment to account for monkeys in the study being exposed for 6 hours a day while the toxicity value being derived is for an exposure period of 24 hours. She stated that it is standard practice for EPA and CalEPA to adjust for exposure time duration, whether in animal or human studies.
  - **Ann V.** explained that the animals underwent continuous exposure over several days, although there may have been periods within each day where they were not exposed. The exposure was repeated day after day, and it's noted that manganese levels do not return to the background immediately. This kind of intermittent exposure was sufficiently relevant.

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- **Daisy D.** noted that unless there's a strong reason not to, it's crucial to adjust the duration from 6 to 24 hours. Tissues may fully recover within shorter periods, and longer exposures can have different effects. Regulatory agencies, like the EPA, routinely adjust for duration in their assessments. This adjustment is essential for accurately interpreting exposure data.

○

## Review Tables in Manganese Framing Document

**Holly Dixon, OHA**, provided a brief refresher on all the different tables in the framing document (slides 32-36). The first table compiles key information on the critical studies used in the TRVs for acute exposure to manganese. Both TCEQ and the petition use the same critical study (Dorman et al. 2005) and Perry et al. use two critical studies (Dorman et al., 2005; Erikson et al., 2008). While TCEQ, the petition, and Perry et al. all use the same point of departure, they all use different uncertainty factors to calculate a 24-hour acute manganese TRV. The differences and similarities in UFs are summarized in Table 2.

Holly then presented Table 3, noting a large portion of it comprises quotes from TCEQ on why they included a database UF. Table 4 includes potential options for DEQ's acute manganese TRV. Holly noted that several of the ATSAC discussion questions relate to the options in this table. She highlighted the last row as an area for members to consider other options that they would prefer over the existing listed options. She concluded by highlighting the last three pages of the framing document go into more detail on considerations for specific UFs.

## Discussion of Key Questions

Ben facilitated the ATSAC members' responses to the prepared discussion questions. He also reminded the members of the discussion worksheet where they can fill out their answers and share them with DEQ. Members were asked the following questions:

1. What critical study option in Table 1 do you like the best and why? Would you propose another option for DEQ to consider?
2. Do you think the  $UF_A$  (interspecies) should be 3 or 10 or something else? Why?
3. Do you think the  $UF_H$  (intraspecies) should be 10 or something else? All proposals in Table 4 have a  $UF_H$  of 10.
4. Do you think the  $UF_L$  (LOAEL) should be 2, 3, 10, or something else? Why?
5. Do you agree with the petitioners that there is enough evidence to not have a  $UF_D$ ? Why or why not? Do you agree with the TCEQ  $UF_D$  of 6? Why or why not?
6. Do you think we should put a cap on the maximum total UF like TCEQ does?
7. What proposal option in Table 4 do you like the best and why? If you do not like any of the options listed in this document, why? Would you propose another option for DEQ to consider? Is there other information that DEQ needs to consider in order to choose a proposal option?

Below are the ATSAC member's responses to the discussion questions.

### John Budroe, CAL EPA (retired)

1. John noted that neither ATSDR nor OEHHA decided to pursue acute toxicity value derivation. ATSDR stated that the available data on the toxicity of inhaled manganese was considered insufficient for deriving an acute intermediate duration inhalation MRLs. Dorman 2005 and Erikson 2008 are not especially good studies; these studies have a freestanding LOAEL with no controls. If

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DEQ needs to derive an acute TRV that is not from a chronic TRV, then Option 4 with cumulative UFs at 1800 is recommended and would result in a TRV of 0.8  $\mu\text{g}/\text{m}^3$ .

2. John recommends using a  $\text{UF}_A$  of a square root of 10. He followed OEHHA REL methodology; a square root of 10 is used for this UF when the data is from non-human primates.
3. John broke his response into two parts: toxicokinetics and toxicodynamics. For toxicokinetics, he suggested applying the square root of 10 to account for residual susceptibility differences and we have some degree of information from PBPK modeling, but it wasn't directly used to develop an internal dose that the TRV is based on. For toxicodynamics, it should also be 10 to account for potential additional susceptibility differences, especially in children; in this situation, both the respiratory system and nervous system can be impacted by early life exposure in children. This should result in a combined  $\text{UF}_H$  of 30.
4. John recommended a  $\text{UF}_L$  of 6 because OEHHA would consider this a mild effect LOAEL.
5. For the  $\text{UF}_D$ , John noted that the framing document highlights that there is substantial uncertainty regarding the potential for neurodevelopmental toxicity in humans. He referenced a study (Takser et al. 2003<sup>[4]</sup>) that found a correlation between higher manganese levels in cord blood and reduced psychomotor development at three years of age, and there are several other human studies that show the potential for neurodevelopmental effects from manganese exposure. This indicates that there is a current lack of animal or quantitative neurodevelopmental data. John recommended a  $\text{UF}_D$  of 3 in all the proposed TRVs as a minimum.
6. As mentioned earlier, OEHHA does not cap cumulative UFs, but does not develop toxicity values for chemicals when the cumulative UF goes over 3,000. John thinks that the IRIS program at the U.S. EPA follows a similar approach. John thinks that a similar approach as OEHHA is greatly preferable instead of capping the cumulative UF at 300 or some other value.
7. Regarding the proposal option, John recommends a cumulative uncertainty factor of 1800, therefore a TRV of 0.8  $\mu\text{g}/\text{m}^3$  is recommended.
- 8.

**Holly D.** mentioned that DEQ and OHA want to know if ATSAC members have concerns with the critical studies in Table 1 and if anyone would prefer if DEQ continues to adapt a chronic TRV for the acute TRV or not have an acute TRV altogether.

**Dave F.** responded to John B.'s comment that these studies are not great, and there are reasons they weren't used to create an acute value. He noted if they didn't use the studies, their option would be to not have a number for acute manganese or stick with a modification of the existing chronic value, and that modification does have a lot of uncertainty.

### **Daisy Dong, CAL EPA**

1. Daisy agreed with combining both studies (Dorman et al. 2005 and Erikson et al. 2008). Daisy notes that a major limitation of these studies is that they have one dose. She said that if DEQ has to come up with an acute TRV, and if the other options are to not have an acute TRV at all or to adapt a chronic TRV, she prefers using the two critical studies in Table 1 (Dorman et al. 2005 and Erikson et al. 2008). The primate studies are preferable over the rat studies due to their greater relevance to humans. The combination of the two critical studies also gives us more information for a regulatory toxicity value than only gene expression or protein level data. Daisy agreed with the 1.5  $\text{mg}/\text{m}^3$  point of departure (POD) value; however, she disagreed with the petitioner's proposal not to adjust for the exposure time duration. Daisy supported incorporating an exposure time adjustment to adjust from 6 hours of exposure to a 24-hour TRV.
2. The interspecies  $\text{UF}_A$  should be 3 because primates are very similar to humans, and essentially already doing the human equivalent concentration calculation. A  $\text{UF}_A$  3 accommodates the possible toxicodynamic differences between monkeys and humans.

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3. Daisy supported an intraspecies  $UF_H$  of 10, which she states is very conventional.
4. She recommended the  $UF_L$  should be 10 as the earlier presentation summarized and given that it is a one dose study.
5. Regarding the  $UF_D$ , Daisy gave weight to the PBPK modeling. Daisy has expertise in PBPK modeling. Every model has uncertainty. However, compared to other chemicals, these manganese PBPK models are actually quite good and included many different variables such as diet contribution and different manganese forms. Daisy liked the approach of modeling 5  $\mu\text{g}/\text{m}^3$  exposure for the different scenarios. At this exposure level, not much change in manganese concentration was observed in the brain. She does not think additional studies are needed for the  $UF_D$ .
6. As John mentioned, Cal EPA does not have a cap on cumulative UFs. In California, when the total UF exceeds 3000, we don't use that critical study because there is too much uncertainty. Daisy suggests avoiding a cap on the UF, because it may lead to an unacceptable level of uncertainty and the data cannot be used.
7. Daisy proposes a new option to include an exposure duration adjustment, which is standard practice. She chooses the same UFs that were selected by the ToxStrategies' group (Perry et al. 2023). Her acute TRV proposal is 1.25  $\mu\text{g}/\text{m}^3$ .

### John Stanek, EPA

1. John noted that Dorman et al. 2005 and Erikson et al. 2008 are the available studies, but they have limitations. It is difficult to call the POD a LOAEL in this case because you have a control and one dose, which is because only one dose was considered during a 15-day exposure period. John expressed uncertainty about whether this information could support setting the LOAEL at 1.5  $\mu\text{g}/\text{m}^3$ . There might be some indication of a NOAEL by looking closely at the two studies. Overall, the database is limited. Modeling could be helpful, but it's crucial to understand how reporting levels in the brain regions might protect against respiratory effects.
2. Not answered at this point in meeting.
3. Not answered at this point in meeting.
4. Not answered at this point in meeting.
5. Not answered at this point in meeting.
6. To reiterate John Budroe's and Daisy's point, when the cumulative UF exceeds 3000, then the EPA will not derive a toxicity value because there is too much uncertainty. Based on John's experience, other agencies do sometimes rely on a single published guideline for acute exposure guideline levels (e.g., OECD, AEGLs). They typically focus on a couple of uncertainty factors like interspecies and intraspecies differences.
7. In agreement with Daisy, a significant concern is the lack of an adjustment to a 24-hour duration. At a minimum 6 to 24-hour duration adjustments should be made, although John is unsure if a 5 out of 7-day adjustment is necessary, considering the study's three-week duration. John noted that he spoke with EPA colleagues about the lack of the 6 to 24-hour exposure duration adjustment and they could not figure out why it was not included; EPA would incorporate the adjustment for any scenario. With uncertainty factors in play, the acute TRV could be either 1.25 or 0.9  $\mu\text{g}/\text{m}^3$ .

### Jeff Fowles, New Zealand Food Safety

1. Jeff acknowledges that relying on a single-dose study is not ideal but after considering that these critical studies include primate data and a fairly well-developed PBPK model, he believes it can work.
2. Jeff stated that the UFs in Option 6 of Table 4 seem reasonable, which is the Perry et al. 2023 option. By supporting Option 6, Jeff recommends a  $UF_A$  value of 3.
3. By supporting Option 6, Jeff recommends a  $UF_H$  value of 10.

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4. Jeff is thinking about the points John S. made about the LOAEL and NOAEL and wonder if more work could be done to explore further reducing the  $UF_L$ .
5. He noted the  $UF_D$  is not justified in this case.
6. Jeff does not support a cap because it is inevitably arbitrary. Even though, as mentioned in the ToxStrategies presentation, UFs may overlap with one another, it is very difficult to tease that apart. UFs may overlap as it's difficult to distinguish between factors and to impose a cap would be arbitrary.
7. Jeff supported Daisy's comment that there needs to be a time adjustment from 6 to 24 hours. If there is no time adjustment, there needs to be good justification as to why not. He recommended a modified Option 6 if there is a time adjustment added.

## Question and Answer

- **John V.** noted the frequency of questions regarding the duration adjustments and suggested asking the petitioners for their reasoning.
- **Holly D.** said that she cannot comment on what the petitioners did, but explained she has found excerpts from TCEQ documents on why a duration adjustment was not included in the TCEQ acute TRV that may help the group. She shared the following quotes:
  - This excerpt is from the TCEQ Manganese Development Support Document<sup>[5]</sup>.
    - "This minimal LOAEL will be applied to exposure durations up to 24 hours of exposure since study data demonstrated that the accumulation of manganese in the lung predominated over the 90-h total, 3-week exposure period."
    - "That is, after 15 exposure days, lung manganese was statistically significantly increased over controls, demonstrating that the toxicokinetic clearance did not occur after each daily 6-h exposure but rather that manganese accumulation in the lung occurred from day to day, and in fact appears to have reached steady state (see table 2 of Doman et al 2005), supporting the use of results from this 90-h total exposure for the derivation of a 24-h value."
  - This excerpt is from the TCEQ Guidelines to Develop Toxicity Factors<sup>[6]</sup>.
    - "If it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute can be used as the 24-h POD. No duration adjustments will be made."
- **Holly D.** asked ATSAC members for their opinions on this. She noted the petitioners likely did not adjust the time if it was reasonable to assume a steady state had been achieved.
  - **Daisy D.** does not think the TCEQ argument is very strong because we do not have the data in this case to know if a 24-hour manganese exposure is completely different from a 6 hour manganese exposure.

## John Vandenberg, Duke University

1. John expressed concern about the modeling's lack of consideration for prenatal and infant exposures up to the age of 3. He mentioned that a sensitive population might be overlooked and referred to the National Institute of Health guidelines on manganese, which outline exposure levels in the diet considered necessary for normal intake but also highlight upper tolerance intake levels for ingestion. He pointed out the significant decrease in upper intake levels for younger children and questioned if the modeling accounts for this. He wondered if this aspect is applied as a  $UF_D$  or  $UF_H$ . However, he's unsure where this fits in exactly, and he's concerned about the lack of data available for infants.
2. John supports a  $UF_A$  of 3.

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3. He supports a  $UF_H$  of at least 10, raising concerns about exposure to prenatal and infants. He notes that the  $UF_H$  could potentially be higher than 10 and is in support of John Budroe's comments on this  $UF$ .
4. Not answered at this point in meeting (see page 16).
5. John is concerned about the lack of data for infants, which could be included as part of the  $UF_D$ .
6. Not answered at this point in meeting.
7. He thinks there should be more discussion on the need for a duration adjustment. He concluded by stating that he doesn't have a definitive conclusion at this point, as different possible options yield  $UF$ s ranging from 900 to 1000 or possibly higher.

### Susan Tilton, Oregon State University

1. Susan was comfortable considering the two studies that were included in the Perry et al. paper that were used to derive the LOAEL for respiratory effects.
2. Regarding the interspecies uncertainty factor  $UF_A$ , Susan agrees with an uncertainty factor of 3. She notes that dosimetry adjustments are not needed in this case and supports a threefold factor for toxicodynamics.
3. She shared support for the intraspecies  $UF_H$  of 10; however, noted some of the data is under consideration in the last  $UF$ .
4. Concerning the  $UF_L$ , Susan understood that part of the rationale for employing a tenfold factor was due to the absence of a 24-hour exposure scenario in the relied-upon studies. She believed there was consideration for this uncertainty incorporated into the decision. Given the single-dose basis, the observed effects leading were identified as mild or reversible.
5. Regarding the  $UF_D$ , Susan reflected on the need for adjustments to assist the potential identification of more sensitive effects if additional studies were accessible. She noted that the PBPK modeling utilized here is quite strong, which incorporates various models, exposure routes, tissue concentrations, and brain regions. However, Susan acknowledged limitations. Susan agreed with other ATSAC members that the modeling is not addressing the full potential for in utero exposure and endpoints. There is uncertainty regarding the most sensitive route of in utero exposure.
6. Not answered at this point in meeting.
7. Susan has not come to a conclusion yet. She said that many of her comments align with Option 6 but has some reservations.

### Questions and Answers:

Ben facilitated further discussion and reflection between ATSAC members.

- **John S.** noted uncertainty on the rationale of the duration adjustment that was in the TCEQ documents. He explained that any exposures via particle inhalation will have some clearance upon cessation of exposure. Steady-state levels reflect exposure with clearance. Even for chronic studies we assume pseudo-steady-state conditions. John stated he does not find the TCEQ argument for no duration adjustment compelling enough. He thinks the bar needs to be high to not do a duration adjustment and he does not see the evidence for that here given such a limited database. It would be highly unusual not to adjust the duration based on guidance from other agencies.
- **Daisy D.** added that for EPA and other agencies' acute guidelines, weekly adjustments from 5 to 7 days are not done, only hourly duration adjustments.
- **Jeff F.** asked what the group thinks about looking at this chemical as a traditional risk assessment exercise with the application of  $UF$ s. Considering manganese is an essential nutrient and systemic exposure would be from the diet, is it beneficial to evaluate the TRV values and determine the level of daily exposure? Given that humans intake this nutrient daily, normal dietary levels range from 1 mg/day to 3 mg/day, with adverse effects expected around 8 mg/day. If the

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proposed TRV is 5 µg/m<sup>3</sup>, and the inhalation rate is 20 cubic meters per day, this translates to about 100 micrograms, which is approximately 10% of the nutritional adequacy daily.

- **Dave F.** highlighted that the route of exposure with manganese is different. All oral exposure goes through the liver, which regulates manganese levels in the body. Humans are intended to ingest manganese and not inhale it to reach nutritional levels.
- **Daisy D.** reiterated that exposure route is an important consideration here and added that ingesting manganese (rather than inhaling it) makes it less likely to end up in the brain. She noted that the PBPK model incorporated the background already from the diet and the air. The background is about 0.5 µg/m<sup>3</sup>. Inhalation of manganese has different effects on the body, particularly the nervous system.
- **Ben, K&W facilitator,** reflected on the discussion and asked members if they had any other comments on the time duration adjustment questions and concerns that had been raised in the meeting.
- **John V.** noted that the duration adjustment is not a UF, it's changing the TRV starting point, the POD. The POD would then be 0.375 ug/m<sup>3</sup> instead of 1.5 ug/m<sup>3</sup>.
  - **Daisy** confirmed that the POD would be reduced to 0.375 ug/m<sup>3</sup> from 1.5 ug/m<sup>3</sup> after applying a duration adjustment from a 6-h to a 24-h exposure duration.
- **John V.** reported out where he is landing for UFs as the meeting wraps up: UFA of 3 because of the monkey data, UFH of at least 10 because he is concerned about exposure to infants and prenatal, and UFL of 10 because it's a freestanding LOAEL. Currently, he is thinking about a total UF of 300 applied following the duration adjustment POD.
- **John S.** agreed that John's UF selections are similar to where he is landing as well. He advised the group that we have to be cautious about what to lump into an UF. John stated that at EPA they try to avoid just trying to bend something into another UF because they are not sure where it fits.
- **John V.** noted that some of these measures are from these studies, and he highlighted the gap in neuro-behavioral study effects.
  - **Holly D.** asked if the lack of neurobehavioral studies fits in the UFD category.
  - **John V.** explained there will always be gaps, and working with primates is good despite them being juveniles. He recommended a UFA of 3 and to add at least 3 for the UFD. He added that he appreciated John S. comment on not co-mingling the different UF categories, but they do relate to each other.
- **John B.** emphasized the lack of neurodevelopmental data and if this does not go into UF<sub>H</sub>, then it should be considered in UF<sub>D</sub>.
- **Holly D.** inquired about the size considerations for those who support UF<sub>D</sub>.
  - **John V.** answered to use 1, 3, or 10.
  - **Susan T.** requested to consider the available reproductive and developmental data that exists that suggests it's not a concern. The focus should be on areas where uncertainty exists and we don't have data, particularly concerning potentially sensitive exposure windows.
  - **Daisy D.** answered 1.
- **John V.** inquired about the nature of the manganese sources in Oregon.
  - **J.R.** responded that the majority of manganese emissions come from biomass boilers, and other sources include foundry operations and shredding metals.

**Ben, K&W facilitator,** thanked everyone for their answers and feedback. He noted that members should feel free to fill out the worksheet and email it to Apple Goeckner at DEQ, noting the instructions are on the worksheet. He reminded the members that the worksheet is optional, but helpful if members fill it out. He asked if there were any final thoughts before moving on to next steps and closing.

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## Closing and Next Steps

**Apple, DEQ,** thanked the ATSAC members for their thoughtful discussion and feedback. DEQ will consider everything they heard. This month DEQ will be writing and editing the meeting minutes from today's meeting and will circulate a draft to members to ensure the minutes are accurate. DEQ will work on a proposal for the acute manganese TRV that will be presented to a rules advisory committee and later to DEQ's governing board, the Environmental Quality Commission. DEQ will keep the members updated on what their proposal will be, likely via email.

Apple also shared information about the next series of ATSAC meetings they will plan once the quality control processes wrap up. DEQ anticipates having a series of at least three meetings in the fall of this year where they will discuss the findings from the TRV review and selection process. Apple noted they envision that at the first meeting, DEQ will orient members to the files/tables prepared for their review. She noted for this meeting, members would not need to do any prep work. DEQ will show the materials they have prepared and answer any clarifying questions. DEQ will plan on the second meeting in the series being a few weeks after the first one so there is plenty of time to review the materials. At this meeting, DEQ hopes to get feedback from members on the overall process that DEQ followed to update TRVs including QC. DEQ also hopes to document ATSAC feedback on the proposed TRVs for individual TACs. The third meeting in the series will reserve more time to discuss other challenging contaminants, like PFAS, diesel particulate matter, etc. Apple will update ATSAC members via email to schedule these meetings. She concluded by thanking members for the great discussion today.

Ben thanked everyone for participating and adjourned the meeting.

<sup>[1]</sup> Proposed TRV Update and Selection Process for ATSAC Review

<https://www.oregon.gov/deq/aq/Documents/ProposedTRVforATSAC.pdf>

<sup>[2]</sup> Framing Document for DEQ's Air Toxics Science Advisory Committee

<https://www.oregon.gov/deq/aq/Documents/ATSAC-ManganesePetition.pdf>

<sup>[3]</sup> Derivation of manganese 24-hour acute inhalation guideline protective of respiratory and neurological effects. <https://www.sciencedirect.com/science/article/pii/S0273230023001861>

<sup>[4]</sup> Manganese, monoamine metabolite levels at birth, and child psychomotor development.

<https://www.sciencedirect.com/science/article/abs/pii/S0161813X03000585>

<sup>[5]</sup> TCEQ Manganese Development Support Document, 2017.

<https://www.tceq.texas.gov/downloads/toxicology/dsd/final/mn.pdf>

<sup>[6]</sup> TCEQ Guidelines to Develop Toxicity Factors,

2015. <https://www.tceq.texas.gov/downloads/toxicology/publications/rg-442.pdf>

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## **Appendix D: Meeting Minutes for ATSAC Meeting #4 on Preparation for TRV Proposal Review**



# Air Toxics Science Advisory Committee (ATSAC)

Meeting 4: January 15, 2025, 11:00am-12:15 pm PT

## Meeting Minutes

### Meeting Attendees

| ATSAC Members          |                                                      |
|------------------------|------------------------------------------------------|
| John Budroe            | California Environmental Protection Agency (retired) |
| John Stanek            | Environmental Protection Agency (EPA)                |
| John Vandenberg        | Duke University                                      |
| Qiaoxiang (Daisy) Dong | California Environmental Protection Agency           |
| Susan Tilton           | Oregon State University                              |
| Project Team           |                                                      |
| Ali Mirzakhali         | Oregon Department of Environmental Quality (DEQ)     |
| Apollonia Goeckner     | Oregon Department of Environmental Quality (DEQ)     |
| Dana Crosby            | Oregon Health Authority (OHA)                        |
| David Farrer           | Oregon Health Authority (OHA)                        |
| Holly Dixon            | Oregon Health Authority (OHA)                        |
| J. R. Giska            | Oregon Department of Environmental Quality (DEQ)     |
| Kristen Martin         | Oregon Department of Environmental Quality (DEQ)     |
| Susan MacMillan        | Oregon Department of Environmental Quality (DEQ)     |
| Facilitation Team      |                                                      |
| Ben Duncan             | Kearns & West                                        |
| Arpana Nautiyal        | Kearns & West                                        |

Meeting slides can be found at <https://www.oregon.gov/deq/eq/Documents/ATSACM4slides.pdf>

### Welcome

**Ali Mirzakhali, Oregon Department of Environmental Quality (DEQ)**, opened the fourth meeting of the Air Toxics Science Advisory Committee (ATSAC) and thanked the ATSAC members for participating in this process and the DEQ and OHA team for their time and effort in developing materials for this meeting.

**Ben Duncan, Kearns & West (K&W) facilitator**, reviewed the Zoom webinar protocols, facilitated introductions from the DEQ-OHA project team, and conducted a roll call of ATSAC members. Ben reviewed the meeting agenda, which included 1) Welcome, 2) Background, 3) Technical Review Updates, 4) ATSAC Document Review, 5) ATSAC Workbook Review and 6) Next Steps and ATSAC Feedback.

### Background

**Holly Dixon, Oregon Health Authority (OHA)**, began the meeting by reviewing background information (slides 5-10). DEQ and OHA are currently reviewing the inhalation TRVs used in DEQ's air quality programs. This is the first time that the state is reviewing and updating these TRVs. The current TRVs were originally adopted into administrative rule in 2018. Currently, they are at the ATSAC step in the

rulemaking process. A standard DEQ rulemaking process includes a Rules Advisory Committee, a Fiscal Advisory Committee, and a Public Comment Period, which will occur later in the process.

Holly also shared the list of sources of toxicity information that DEQ considers to be authoritative in terms of their scientific rigor and comprehensive methods for producing toxicity information. These “authoritative sources” are the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency (EPA), California Environmental Protection Agency (CalEPA), and Oregon DEQ in consultation with the ATSAC. These authoritative sources are in Oregon Administrative Rule, which were adopted by DEQ’s governing board (the Environmental Quality Commission). In 2021, Oregon DEQ in consultation with ATSAC was added as an authoritative source, meaning that DEQ in consultation with ATSAC can develop TRVs and consider TRVs developed by organizations other than U.S. EPA, U.S. ATSDR, and CalEPA. Holly reviewed the ATSAC’s role, which includes advising DEQ and OHA on the development of TRVs, reviewing and providing feedback on TRVs proposed by DEQ, and recognizing scientific uncertainties and the development of new information in the field related to DEQ’s TRVs.

Holly also reviewed the previous three ATSAC meetings and reminded the committee members that all previous meeting materials are available online on the [ATSAC website](#). The first ATSAC meeting in October 2022 was an orientation that covered information about DEQ’s air quality regulatory program, TRV definitions, and the purpose of the ATSAC. The second ATSAC meeting was held in January 2023 and during this meeting the ATSAC members provided feedback on the DEQ-OHA project team’s plan for reviewing and updating DEQ’s inhalation TRVs. This feedback was very helpful and the team made changes to the overall TRV review process in response to that feedback, and these changes are summarized in [this document](#). For example, ATSAC members recommended that the DEQ-OHA project team should gather additional TRV information to inform TRV selection, such as point of departure method and information on time adjustments. The DEQ-OHA project team has added this information to the TRV review tool and collected all this information on each candidate TRV. The ATSAC members also requested to see all the candidate TRVs along with the one DEQ is proposing for selection, and the team has incorporated this information into the ATSAC workbooks. The third ATSAC meeting was held in April 2024. During this meeting, the DEQ-OHA project team gathered feedback from ATSAC members on a petition to change DEQ’s manganese TRV for acute exposure. After receiving this feedback during and after the meeting, the agencies developed a proposal for the acute manganese TRV. The team prepared [a memo on DEQ’s proposal](#) which was sent to the ATSAC members and posted online in Summer 2024. The purpose of this fourth ATSAC meeting was to kick off the current series of ATSAC meetings to discuss the overall TRV update process and specific TRV proposals.

#### Questions and Discussion:

- **John Vandenberg:** Are there opportunities for public comment throughout the ATSAC and DEQ rulemaking process, or is it only at the end of the process? Will the ATSAC hear any public comments?
  - **J.R. Giska:** The DEQ-OHA project team is seeking to limit direct interaction for the ATSAC with questions and comments from the public since the ATSAC members are volunteers whose role is focused on providing technical input. OHA and DEQ will bring proposals consulted on by the ATSAC to a Rulemaking Advisory Committee (RAC), which will review those materials and have a public comment period. If issues arise during the RAC

that need to come back to the ATSAC for clarification, the project team will lead that process as needed.

- **J.R.:** The rules also allow for a petition process, which is another way that non-ATSAC members can contribute to the process. Thus far, one petition was received to adjust the manganese acute TRV value, which the ATSAC discussed in Meeting #3.
- **John V.** asked clarifying questions about the concentrations and definitions for the TRVs. Is the TRV equal to a one in a million cancer risk? Is the non-cancer TRV equal to a reference concentration?
  - **Holly:** The team will recirculate a fact sheet that includes DEQ's definitions for chronic non-cancer, acute, and cancer TRVs to ATSAC members:  
<https://www.oregon.gov/deq/aq/Documents/ProposedTRVforATSAC.pdf>.

## Technical Review Updates

Holly reviewed the technical review work that the team has conducted since ATSAC Meeting #2 in January 2023 and shared an overview of the proposed TRV changes with the ATSAC (slides 12-15). This work included the following categories and tasks:

- TRV Tool Revisions:
  - Integrated ATSAC feedback
  - Revised the TRV tool to contain more derivation parameters on candidate TRVs
  - Tested the TRV tool
  - Identified the starting list of 600+ air contaminants
- TRV Data Entry:
  - Searched for TRV info from authoritative sources
  - Searched additional sources for TRVs for high priority contaminants
  - Modified or adopted 184 TRVs from other sources where necessary
  - Selected TRVs for proposal when multiple candidate TRVs were available
- Quality Control:
  - Designed a quality control process
  - Hired Eastern Research Group (ERG) to do the quality control work
  - Reviewed ERG feedback
  - Integrated revisions into the TRV Tool
- Review Material Development:
  - Planned a suite of materials to help ATSAC review the TRV proposals
  - Wrote eight supporting documents for ATSAC
  - Created two Excel workbooks for ATSAC
- Process Development & Project Management

Overall, the state is proposing a total of 624 TRVs for 377 toxic air contaminants. Of these 624 TRVs, 51% of these TRVs are the exact same as the TRV from 2018. 32% of the 624 proposed TRVs are new TRVs, meaning that there was no TRV in 2018. The remaining 17% of the 624 TRVs are different from the 2018 TRV. There are 238 proposed TRVs where TRV information was available from more than one authoritative source. In response to feedback at ATSAC meeting #2, we put together an excel workbook where we highlighted cases where there were multiple candidate TRVs available to choose from and

provided derivation information for each TRV candidate and highlighted the TRV we selected for proposal. In addition, there are 184 proposed TRVs where “DEQ in consultation with ATSAC” is the authoritative source. The OHA-DEQ team is requesting consultation with ATSAC members on these 184 proposed TRVs.

DEQ and OHA’s request of the ATSAC members is to carefully review the documents and workbooks related to the TRV review and be prepared to share answers to the discussion questions during the upcoming ATSAC meetings. If the ATSAC members have any questions, they are encouraged to reach out to agency staff via email.

## ATSAC Document Review

Holly reviewed the documents that the DEQ-OHA project team has prepared and provided to the ATSAC members (slides 19-20). The team showed where these documents are located on the [ATSAC website](#) and provided an overview of each of the documents and their purpose. These documents are listed and linked below:

- [Document 1: Overview of TRV Review](#)
- [Document 2: Quality Control of Toxicity Reference Values](#)
- [Document 3: ATSAC Meetings #5-7 Discussion Questions](#)
- [Document 4: Proposed TRVs Where DEQ is the Authoritative Source](#)
- [Document 5: Proposed Groupings of Toxic Air Contaminants](#)
- [Document 6: Proposed TRVs Using PPRTV Screening Values as the Authoritative Source](#)
- [Document 7: Proposed TRVs Not Yet Finalized by Authoritative Sources](#)
- [Document 8: Diesel Particulate Matter \(DPM\) Framing Document](#)

### Questions and Discussion:

- **John V.** asked how new updates to TRVs from authoritative sources or other updates or revisions to scientific documents can be reflected or incorporated in the workbooks over time.
  - **Holly:** The DEQ/OHA team is tracking TRVs that are not yet finalized and are in draft or public comment mode. In Document 7, the team lists the cutoff date used to prepare for these ATSAC meetings and their proposal for handling them. The team is interested in ATSAC feedback on that intended process.
  - **John V.** suggested including a column to the table in Document 7 with the date so it is possible to update the values in response to new information and track those changes.
- **Daisy Dong** asked whether the DEQ/OHA team is looking for the ATSAC members to check the calculations in Document 4 and the workbooks for any errors.
  - **Holly:** The team is primarily looking for ATSAC member feedback on the overall process and approach for TRV adjustments and modifications. The team tried to do quality control and double check the calculations before sharing these materials with the ATSAC. While the team would appreciate the ATSAC members sharing if any errors are found, they want to be mindful of the ATSAC members’ time and request that the majority of review time is spent on the overall process.

## ATSAC Workbook Review

Holly reviewed the Excel workbooks that the DEQ-OHA project team has provided to the ATSAC members (slides 22-23). These workbooks are listed and linked below:

- [ATSAC Workbook 1: DEQ Proposed TRVs](#)
- [ATSAC Workbook 2: TRV Derivation](#)

Workbook 1 and Workbook 2 share different information about the TRV proposals. Workbook 1 is a broad overview of all proposed TRVs and is anticipated to be used as a quick reference when reviewing documents. Workbook 2 includes more detailed derivation information, and the purpose of this workbook is to share detailed information about the derivation of inhalation TRVs. This workbook also highlights when there were multiple candidate TRVs available to choose from and which TRV option DEQ is proposing.

The first tab in each workbook is the Information Tab, which includes a description of the purpose of the document and an explanation of each subsequent tab and is the best place to refer to if you have questions about the content on a tab. The information in the workbooks is color-coded with blue representing cancer, yellow representing chronic noncancer, and green representing acute noncancer TRVs. The ATSAC members are requested to review Tabs 2-4 of Workbook 2, which contain only toxic air contaminants that have TRVs available from more than one authoritative source and a TRV that DEQ is proposing to change from existing 2018 rule. ATSAC members can record their feedback in Document 3 and/or in the ATSAC comment column on the workbook tabs. The appendices (tabs 5-6) are provided as a reference if ATSAC members have derivation questions while reviewing other documents.

### Questions and Discussion:

- **John V.** asked if the ATSAC members should provide concurrence or affirmation with the approach in their notes in addition to noting any concerns or issues.
  - **Holly:** Yes, it would be helpful for ATSAC members to provide feedback in either direction to note that ATSAC members have reviewed the information and how they feel about the DEQ/OHA team's proposed process.
  - **Holly:** There are multiple ways that ATSAC members can record their notes and provide feedback, including the discussion questions document and the ATSAC Notes column in Workbook 2. ATSAC members can use whichever resource is most helpful for them to record their thoughts.
- **John V.** asked if a change made in one of the workbooks will automatically populate the other workbook.
  - **Holly:** No, the workbooks are separate.
- **Daisy** clarified that Workbook 1 is a summary table of the proposed values while the detailed information on the derivation process is provided in Workbook 2, and asked if the ATSAC members should focus their review on Workbook 2.
  - **Holly:** Yes, Workbook 1 is a broader overview and should be a helpful resource while Workbook 2 provides more detailed TRV derivation information, especially if you would like to see percent change from the 2018 value. It is important for ATSAC members to

spend time reviewing and providing feedback on Tabs 2-4 of Workbook 2 because there are multiple options that DEQ is selecting from, and they are changing from 2018.

- **David Farrer, OHA:** Only chemicals that meet certain criteria are in the colored tabs of workbook 2, e.g., there were multiple TRV options to select from. The appendices have the derivation information for all of the TRVs. In Workbook 2, filtering is helpful, but sorting will make the formatting more difficult to review.
- **John Stanek** asked whether the workbook copies are shared or downloaded.
  - **Holly:** Each ATSAC member has a downloaded copy of their own workbook, and the team would appreciate receiving a copy with individual ATSAC members' comments at the end of the process.
  - **Susan:** What are the next steps for this process? What is the focus of the next ATSAC meetings?
  - **Holly:** Clarified this will be covered in the next section.

## Next Steps and ATSAC Feedback

Holly reviewed next steps for the ATSAC members and the upcoming series of ATSAC meetings (slides 26-27). The upcoming ATSAC meeting agendas will follow the discussion questions in the same order that they appear in Document 3. ATSAC members were encouraged to reach out to Holly and David with OHA if they have any questions and provided their contact information.

Ben thanked everyone for participating and adjourned the meeting.

**Appendix E: Meeting Minutes for  
ATSAC Meetings #5-7 on the Review of  
TRV Proposals**

# Air Toxics Science Advisory Committee (ATSAC)

## Meetings #5-7

### Meeting Minutes

#### Meeting Attendees

| ATSAC Members          |                                                      |
|------------------------|------------------------------------------------------|
| John Budroe            | California Environmental Protection Agency (retired) |
| John Stanek            | Environmental Protection Agency (EPA)                |
| John Vandenberg        | Duke University                                      |
| Qiaoxiang (Daisy) Dong | California Environmental Protection Agency           |
| Susan Tilton           | Oregon State University                              |
| Project Team           |                                                      |
| Apollonia Goeckner     | Oregon Department of Environmental Quality (DEQ)     |
| Dana Crosby            | Oregon Health Authority (OHA)                        |
| David Farrer           | Oregon Health Authority (OHA)                        |
| Holly Dixon            | Oregon Health Authority (OHA)                        |
| J. R. Giska            | Oregon Department of Environmental Quality (DEQ)     |
| Kristen Martin         | Oregon Department of Environmental Quality (DEQ)     |
| Susan MacMillan        | Oregon Department of Environmental Quality (DEQ)     |
| Facilitation Team      |                                                      |
| Ben Duncan             | Kearns & West                                        |
| Angela Hessenius       | Kearns & West                                        |

Meeting slides can be found at <https://www.oregon.gov/deq/aq/Documents/ATSACm5-7Proposals.pdf>

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#### ATSAC Meeting #5: February 10, 2025, 10:00am-1:00 pm PT

#### Welcome

**Ben Duncan, Kearns & West (K&W) facilitator** reviewed the Zoom webinar protocols, facilitated introductions from the DEQ and OHA project team, and conducted a roll call of Air Toxics Science Advisory Committee (ATSAC) members.

**JR Giska, Oregon Department of Environmental Quality (DEQ)**, thanked the ATSAC members for their participation and reviewed the overall toxicity reference value (TRV) review and rulemaking process. This process includes reviewing authoritative sources, developing proposals, and bringing those proposals to the ATSAC for review and discussion. JR reminded the group that the ATSAC is not a decision-making body, and that their purpose is to provide input and feedback on DEQ and OHA's proposals. The formal rules process will begin later on in the process, and this will include a public process including a rulemaking advisory committee comprised of members of the public and a public comment period.



**Holly Dixon, Oregon Health Authority (OHA)**, reviewed the agenda for the meeting, which included 1) Welcome, 2) ATSAC Discussion, and 3) Next Steps. Holly also outlined the current series of ATSAC meetings, which includes Meeting #5, Meeting #6 (February 11), and Meeting #7 (February 19). Meeting #8 will focus on discussing diesel particulate matter and that meeting is anticipated to be scheduled in May 2025.

Holly shared that the focus of this meeting will be to discuss the ATSAC discussion questions in [Document 3: ATSAC Meetings #5-7 Discussion Questions Worksheet](#).

#### Questions:

- **John Vandenberg:** Is it correct to assume that ATSAC members' written comments will be available to the public in future steps of the TRV review process?
  - **Holly:** Anything that the ATSAC members provide in written form will be compiled and that compiled document will be posted online and provided to subsequent committees. There will also likely be a document that compiles the changes that were made to the original proposals in response to the ATSAC's comments and feedback.

## ATSAC Discussion

### Overall Process Questions

The ATSAC members discussed the following questions:

#### 1. Do you feel prepared to go through these discussion questions?

#### 2. What was your experience like preparing for this review process as an ATSAC member?

#### 3. Do you agree with DEQ's and OHA's overall process for reviewing and updating TRVs?

- **John V.:** Providing links to source materials was really helpful. There is a lot of information provided, and it is helpful to split the discussion across different sessions. The clarity of communications is very impressive, and the materials are well-organized and coherent, which makes the large volume of information easier to understand.
- **John V.:** In some cases, there was a lack of clarity around how the team is handling rounding and significant digits. The clear characterization of the approach for handling significant digits is important because the rounding leads to differences in results from doing the calculations.
  - **David Farrer (OHA):** The team's process was that they used all digits in every calculation step for the derivation process until reaching the final TRV. At the TRV step, they rounded to two significant digits.
  - **John V.:** In some cases, the TRVs are presented with one significant digit instead of two significant digits. That could be interpreted differently by different people.
  - **David:** In some cases where a TRV was adopted from another agency, if they presented a TRV with one significant digit, the team used the value as they presented it. The ones that the DEQ-OHA team derived themselves, they used the process just described.
  - **David and Holly:** The team will make their process clearer in their documentation.

- **John Budroe:** Asked for clarification on whether the ATSAC's primary charge is to review and provide feedback on the overall TRV process and how the TRVs were developed or to review all the TRVs one-by-one. With approximately 300 chemicals, it is a bit unrealistic to be able to review every TRV in the timeframe provided. A lot of discussion time could be spent on carcinogenic polycyclic aromatic hydrocarbons (PAH) relative potency factors (RPFs) because what Minnesota Department of Health has done is based on 2017 IRIS, and CalEPA also has its own RPFs for PAHs, some of which are relative to benzo(a)pyrene unit risk, but some of which are on their own. Comparing the different systems for generating RPFs could be a lot of discussion. Another topic that could take up a lot of discussion is the new World Health Organization (WHO) toxic equivalency factors (TEFs) for dioxins and furans.
  - **Holly:** The team recognizes that they have provided a lot of information to the ATSAC members, and the team has thought about how they can highlight specific items for review and acknowledge that some individual questions will require more discussion time. The overall charge of the ATSAC is to first review and provide feedback on the overall process and quality control process, and then bring attention to specific questions related to specific TRVs. Most of these questions are included in the supplemental documents provided to ATSAC members, with an emphasis on [ATSAC Document 4](#) which covers the TRVs that list DEQ in consultation with ATSAC as the authoritative source. These questions were grouped by main themes and categories so that ATSAC members could comment on the overall process and apply that feedback to specific TRVs as needed.
  - **Holly:** The DEQ-OHA team encourages the ATSAC members to let them know if certain topics will need additional discussion time.
  - **John B.:** There will be pros and cons for each system for doing relative potencies for PAHs, and it would be helpful to discuss those differences.
  - **Holly and David:** The ATSAC will have a specific conversation on PAHs under Discussion Question #6 for Document 4. The team will make space for this conversation and go into detail on the questions that John B. has posed.
  - **JR:** The detailed conversations on specific TRVs will be especially important for the TRVs that DEQ in consultation with the ATSAC will be the authoritative source for.
- **Daisy Dong:** Shared appreciation for the amount of work that the team put in and noted that all the necessary information has been provided in the materials. There are so many chemicals that the information is overwhelming and could be presented in a more focused way. Rearranging the way that the information and data is organized could simplify the review process, support ATSAC members in working through the information and approaches in a more systematic way and help support transparency. In the future, the materials could be updated to consolidate to one document and on Excel sheet; this would also make the process of updating or making any changes easier. Another potential way to streamline the TRV review process is to allocate certain chemicals to each ATSAC committee member to divide the work among members and allow each member to focus on the chemicals that they have specific expertise in.
  - **Holly:** Thanked Daisy for these suggestions and shared that the team is open to any ideas and feedback on how they can best organize this information for future steps in the process.

- **Susan Tilton:** Appreciated the information provided and noted that the references and links included in the document were very helpful. The questions get very specific about commenting on individual TRVs, and it was difficult to make comments at that level given the number of chemicals due to time constraints, particularly for areas where there was not an overall process to be evaluated. Also appreciated that a lot of the comments received from the ATSAC so far were taken into consideration, such as providing all available TRV values from other sources in the materials, which was very helpful.
- **Susan:** The tables in Document 4 are well referenced with where information comes from, but when you look at the workbook, a lot of what is provided in Document 4 only has DEQ listed as the source. How is all the other information provided to the ATSAC going to be connected back to the workbook so that it will be possible to track the original sources of information? Is the workbook the primary document that individuals will go to for TRV values and will the public have access to the information that the ATSAC has?
  - **Holly:** Right now, Document 4 is presented as an ATSAC document. After the DEQ-OHA team receives feedback from the ATSAC, there will be documentation that will show the derivation for the TRVs where DEQ in consultation with ATSAC is the authoritative source for future committee processes.
- **Susan:** What is the process for draft or lower confidence values as new values are confirmed? Is there a cutoff date for including new information, or is this a living document that will continue to be updated as new values are confirmed, or would updates need to happen in consultation with the ATSAC?
  - **Holly:** It was challenging to prepare all of the materials for the rulemaking process and meetings with the ATSAC because the values are changing with some TRVs that are not final and are in draft. The team had to have a cutoff date in order to have final numbers to write the documents. The DEQ-OHA team incorporated all new updates to the inhalation TRVs from all authoritative sources as of August 8, 2024, which included information that was not yet final. In early December, the team checked the list of draft TRVs to see if any had been finalized. These dates are in [ATSAC Document 7](#). The team acknowledges that these values will continue to be updated during the rulemaking process and their anticipated process is to continue monitoring and taking a close look at new TRVs and updates to TRVs and evaluate them on a case-by-case basis before the public comment period of the rulemaking.
  - **John V.:** Suggested including some information to clarify the timeframe in the overview document and consistently provide the cutoff date used in each document. Each document should include the date it was updated and make it clearer what the process was for incorporating new values, both to this point and moving forward.
  - **Holly:** The team will add the cutoff dates for the information sources used to the overview document to make that clearer and keep the version dates on all the documents that are available to the public on the website accurate.
  - **Holly:** The frequency of the overall TRV review process is specified in Oregon administrative rule and is currently a triennial review process.
  - **Daisy:** Suggested adding a column to Workbook 2 with the date so that when values are updated or finalized the team can simply change the date in that column.

- **John Stanek:** Appreciated the organization for the review; the separate documents have been helpful. Agreed with other comments about the importance of transparency and making sure that it is clear how the TRV derivations were done, especially for values that DEQ is proposing as the authoritative source.

#### 4. Do you have any questions related to the Overview of TRV Review document ([Document 1](#))?

- **John V.:** It would be useful to include the definitions of the chronic cancer TRV, chronic non-cancer TRV, and acute non-cancer TRV that the DEQ-OHA team is using in the overview document. There is an assumption that the values pulled from other authoritative sources are using the same definitions, and it would be helpful to include these definitions and be as clear as possible about what these terms and their interpretations mean.
  - **Holly:** The team will bring those definitions to forefront and include them in Document 1 (or as an attachment to Document 1).
- **John B.:** Agreed with John Vandenberg's comment and noted that it is important to note differences between how Oregon is defining and expressing these values compared to other sources.
- **John S.:** Suggested adding a sentence or two about data gaps, highlighting the number of reference values that are missing or for how many chemicals there was not a TRV.
- **Susan:** What were the parameters considered in the TRV selection process? Was it just the most recent value or were there other considerations and a process for determining that?
  - **Holly:** The team had originally proposed to use the most recent publication date, but during ATSAC Meeting #2, committee members shared feedback that it would be better to look at different attributes of the TRV and review the derivation process more holistically and comprehensively to choose the best option for Oregon's program. The team made a list of preferred TRV attributes for both chronic and acute, which was outlined in this document: [Updates to the TRV Update and Selection Process after the ATSAC Meeting on January 20, 2023](#), which the team will recirculate to the ATSAC. When the team made their selections from available TRVs, the preferred attributes included whether it included a new critical study, modern point of departure (POD) methods, uncertainty factors informed by new studies, as well as publication date.

#### 5. Do you agree that the quality control (QC) process was adequate ([Document 2](#))?

Holly shared that this document was developed by Eastern Research Group (ERG), who DEQ and OHA contracted with to check all the work completed in developing the TRV tool. The team solicited feedback from ATSAC members on whether this quality control process was adequate and whether they had any feedback for this and future processes.

- **John V.:** What is the purpose of commenting on this document if it has been completed? What would happen if comments were made suggesting changes or revisions to this document?
  - **Holly:** Depending on what the comments are, if concerns are identified, the team will go back and look to brainstorm how those could be addressed during this rulemaking or could brainstorm for how they could change this process for the future.

- **John V.:** Is it a correct reading of the document that one ERG analyst reviewed each of the chemicals, and it was only elevated to a second reviewer if an error was identified that would impact the TRV derivation or was otherwise substantial.
  - **David:** That is correct for ERG’s review process. There was also an additional step; the DEQ-OHA team conducted spot checks as they went.
  - **John V.:** Suggested that the Oregon state agencies consider creating their own document outlining the QC process that includes the ERG document as an attachment. That would allow the state to include a fuller picture of the QC design process and show the full amount of work that was completed to ensure quality. In general, the process that was described seemed appropriate but may not be a complete account of what the state did. It is also a bit unclear how the analysts decided whether an error was deemed “substantial” and therefore elevated to a second reviewer. It also may be helpful to add other information, such as rounding conventions (raised in the discussion of Overall Process Question #3).
  - **David:** The team can add more clarity to improve this document. One of the criteria for what is meant as “substantial” is if the error or discrepancy found would change the TRV value.
- **John B.:** Agreed with John V.’s comments and thought in general that the QC process was good.
- **Susan:** Did not have any concerns with the QC process. There is a portion of the QC process that is on confirmation of the hazard index designation. Is that an integral part of the TRV derivation?
  - **Holly:** The team had the contractor review some pieces of information that the state was collecting for the hazard index process which is a separate process related to the regulatory Cleaner Air Oregon program at DEQ. There is a policy where the state has to assign non-cancer TRVs a hazard index of 5 or 3, and different regulations apply depending on the hazard index. A few years ago, a technical advisory committee helped the state determine what the criteria are for the hazard index designations, including whether there are any reproductive or developmental health effects or if it is on the Oregon Department of Transportation’s list. The team provided a fact sheet on the [Cleaner Air Oregon’s Hazard Index Rule Requirements](#) for ATSAC members to reference. At this time, the team is not asking the ATSAC members to review these hazard index assignments since they were already reviewed by a separate technical advisory committee focused on this.
- **Daisy:** The QC process was adequate. One concern was whether any errors might have been introduced from transcribing the numbers from the original source document into the workbooks. Has the team done any QC for the Excel workbooks?
  - **JR:** The team used macros based on the same tables to create both workbooks, so that mitigates the risk of transcription errors. There were checks involved in the coding process, so the team feels confident that the values in the workbooks are correct.
  - **David:** The team also checked the workbooks for row shift errors and conducted spot checking of the workbooks.

## ATSAC Workbook Questions

The ATSAC members discussed the following questions:

**1. Did Workbooks 1 and 2 capture the right information?**

**2. Did you identify any systemic or thematic problems with either workbook that could be improved?**

**3. Are there any missing functionalities in Workbooks 1 or 2 that should work differently that we could improve for the next time we do TRV updates?**

**4. Were you able to access all the information you needed to make decisions about whether to support DEQ's proposed TRVs?**

- **Daisy:** Provided suggestions to rearrange the way the information is presented in Workbook 2 to improve transparency by showing the whole process and allow the ATSAC members to follow along with the TRV calculations as they review. The columns in the workbook could be rearranged to show the critical effect (this would include the specific duration), point of departure (NOAEL or LOAEL) (including the actual POD value), time adjustment, human equivalent concentration (HEC) value, and end with uncertainty factor. If formatted this way, this would allow the ATSAC members to check that the TRV derivation calculations have been done correctly.
- **Daisy:** On the worksheet for cancer TRVs, the column is listed as a "source TRV." It would be more accurate to say, "Source Inhalation Unit Risk (IUR)" and include the IUR, since DEQ uses a one in one million definition while some sources use one in 100,000. That way, ATSAC members can support QC by checking whether the IUR is correct or not.
- **Daisy:** Suggested including the information that is provided in Workbook 1 (percent change of proposed TRV value compared to 2018 value). It would be helpful to have one central document to review so that all the information can be provided in one place. The chemicals can be sorted alphabetically but showing the percent change can help highlight which chemicals the ATSAC members should pay special attention to in their review; certain chemicals could also be highlighted for this purpose. This way, ATSAC members can review the selection criteria and understand and provide feedback on the reasons why there are any significant changes.
- **Daisy:** In the future, recommend organizing the guiding documents as different sections of the same document with each section having rules, so that it functions as a standard operating procedure (SOP). If the ATSAC members review and agree with all of the rules, then they do not need to check each TRV individually. In the workbook, there can be a column where each TRV refers to the rule that the TRV selection was based on and includes a link to that rule. In the future, if the rules are changed, the values can be updated based on the new rule. ATSAC members can also review and flag any chemicals that they think do not fit the rule that was applied. For Workbook 2, the ATSAC members cannot QC the information because the source POD is not provided (need to include the POD value in the workbook). As currently set up, Workbook 2 and Document 4 repeat the same information, rather than having one central document. Daisy offered to meet with the team outside of this meeting to further discuss how to simplify the organization of the documents. For future ATSAC members, only two documents would be needed: an SOP and a worksheet.
  - **Holly:** Appreciated this feedback on how the team can restructure the information, it is very helpful.

- **David:** It would be helpful to send a copy of Workbook 2 with these recommended changes so the team can review how it looks.
- **David:** A lot of the reasons for why the team selected one TRV over another are provided in Workbook 1 in the *Reason for Change* column in a short, condensed version. It might be helpful to expand that.
- **Daisy:** Recommend having a master Excel spreadsheet with all the information, and the team could create an external version by hiding any irrelevant information. For the calculation sheets, it may also be helpful to create a password protected version so that only certain people have access to that sheet. The team can QC the master workbook to make sure all the information is accurate, and from there create any output they need.
- **Daisy:** In the materials, where it states that if the dosimetric adjustment factor (DAF) equals one there is no human equivalent concentration (HEC) adjustment; that is incorrect. As long as you use the DAF, even if it is one (e.g., RGDR = 1 or systemic effect = 1), that is an adjustment of a human equivalent concentration. If you do not use a DAF, then your interspecies uncertainty factor (UF) is ten. If a DAF is used, it does not matter if the value is one or not, it will reduce the interspecies UF. Most agencies reduce the interspecies UF for toxicokinetics all the way from three to one if there is an HEC adjustment, but OEHHA usually reduces it from three to two to cover the toxicokinetic (TK) difference.
- **Daisy:** In the materials it also states that OEHHA's REL value was used for the 1-hour POD in some cases. This is not conceptually correct. If OEHHA already adjusted their POD with uncertainty factors to calculate their REL, it is confusing to use their REL as the source POD; recommend taking the source POD and applying the UFs applied by the authoritative agency to the downstream calculation.
- **Daisy:** There is one typo in Workbook 1 on the first sheet that should be corrected where it states "acute" instead of "chronic."
- **John V.:** Shared appreciation for the effort and amount of information compiled, and shared that it was useful to have Workbooks 1 and 2. Noted that he conducted spot checks and focused mostly on cancer values. Recommended adding a date stamp to each row so it is clear when that chemical was evaluated and in case there are any updates. It would also be useful to include the inhalation unit risk value (IUR) that was used for the cancer TRVs.
- **John V.:** For many of these carcinogens, the age-dependent adjustment factors that are frequently used now were not included and not applied. The application of these age factors yields about a 60% increase in lifetime risk. From the adoption of guidelines in 2005 or 2006, the age-dependent adjustment factors have been applied in the IRIS program. In some cases, California has also applied a factor for early life exposure. It would be useful to note for which chemicals these age-dependent adjustment factors were applied to. Assuming that the State is not proactively adding age-dependent adjustment factors to the older carcinogen assessments.
  - **David:** The state applied the early life adjustment factor to chemicals with a mutagenic mode of action (not all carcinogens), including formaldehyde from the most recent IRIS assessment. There is a column in the workbook where it is noted whether carcinogenic chemicals have a mutagenic mode of action or not, but the team will think about how to mark these chemicals more clearly and consistently. The early life adjustment factors are applied when the TRVs are converted into a risk-based concentration (RBC). The

state has been saving the RBC component for the rules advisory committee, and they have other adjustments that will be applied as well, such as multi-pathway adjustment factors. It could be valuable to flag the TRVs in the workbooks for any of these adjustments that will be applied to the RBC.

- **John V.:** This would also need to be accompanied by a document explaining what the state did and under what conditions.
- **John V.:** Many of the carcinogens with earlier assessments also likely have a mutagenic mode of action, but this would not have been applied retroactively.
- **John B.:** California is taking a similar approach to the early life adjustment factors where they do not apply them in the risk assessment but apply them in the risk management analysis. For example, it would be included in the guidance manual for the hotspots program along with multi-pathway and other adjustments. In contrast to Oregon, California does not apply the early life adjustment factors only to genotoxic carcinogens but rather applies them to all carcinogens.
- **David:** Oregon applies the early life adjustment factors only to mutagenic genotoxic toxic air contaminants (TACs), which is the approach EPA also takes. This is a policy decision.
- **John V.:** Moving the workbooks into an online system that has a user-friendly, dynamic interface and is searchable for specific chemicals could be useful for the public in addition to the workbooks for future steps in the process.
- **John B.:** Agreed with Daisy's recommendation to add a column with the POD to the non-cancer TRV tabs in the workbooks, and also recommends adding a column with IUR and/slope factor for the cancer TRV tabs.
- **Susan:** Appreciated how much information is consolidated in the workbooks. Agree with other comments that it would be helpful to move any information that is currently only in Document 4 such as PODs or other factors that are used in calculations, so that all the information is in one centralized location. Used the workbooks primarily as a reference to spot check or understand a specific example in Document 4.
- **John S.:** Agree with Daisy's idea for some reorganization and restructuring. In the language within the actual documents, there seems to be some conflation between DAF language and HECs and whether or not a default of one is used.
- **Daisy:** Recommended specifying what species of animal (e.g., mice, rabbit, etc.) were used in the studies. EPA has some calculation errors for rabbit, so it might be worthwhile to check the inhalation rates for those TRVs.
  - **John V.:** Going back through and identifying the animal species could be a significant effort since it entails going back into each of the documents again. Asked if these comments need to be balanced against the need to continue moving the process forward. Some of the comments may be straightforward to address, while others would be a larger effort.
  - **Holly:** The DEQ-OHA team will likely take these comments and bucket them into two categories for changes that need to be made for this rulemaking process and other changes that the team can make for the next time they complete this review process.



- **John V.:** Agrees with that approach and shared that in his view, the materials are adequate to move the program forward and applying it. There will likely be additional improvements suggested during the public comment process and some of them will be simple and straightforward to apply whereas others will not, but it is important to avoid any significant delays to the process.

## ATSAC Discussion

### Questions on Document 4

Holly introduced this section and shared that these questions on Document 4 are more focused on specific TRVs and less focused on process compared to the previous discussion questions. The ATSAC discussed each of these questions one-by-one.

#### 1. What feedback or concerns do you have about the way DEQ proposes to adjust acute TRVs for exposure time in many cases (Section 2)?

- **Daisy:** Why did the team choose to adopt OEHHA's 1-hour reference exposure level (REL) rather than OEHHA's 8-hour REL to base the duration adjustments on to calculate their 24-hour acute TRVs?
  - **David:** OEHHA's 8-hour REL is more of a chronic than an acute value. This REL is based on a scenario of eight hours of exposure every day.
  - **John B.:** That is correct, the 8-hour REL is a special case of the chronic REL designed to protect off-site workers that are exposed eight hours per day for five days per week, so it is a different application than the acute REL.
- **Daisy:** In Table 1, suggested converting at the POD level from the volumetric unit used in animal studies (e.g., ppb, ppm) to microgram per cubic meter. This provides a sense of the magnitude of the human TRV compared to the animal POD, so it is preferable to doing the conversion at the end. Also suggest adding the molecular weight for the unit conversion; this format is more clear and easier to check whether it is correct.
- **Daisy:** For bromomethane, the Haber's Law exponent "n" value was used (n=1.33), but when using Haber's Law, an empirically derived exponent "n" should not be used if the target exposure duration is outside the tested time window in the empirical study. In other words, you should not extrapolate beyond the empirical data. If it is outside that window, it may be more appropriate to use a default value of one, depending on the original source study where the 1.33 was derived.
- **Daisy:** Document 4 states that the POD = OEHHA's 1-hour REL, but this could be confusing. Would rather do the POD/UF here.
- **John V.:** Thought this section was well described. There is a foundational document about acute risk assessment methods that would be helpful to include as a reference document.
  - **John S.:** An OECD Work Group developed a [guidelines document for acute risk assessment](#) that talked a lot about duration adjustments with some case studies.
- **John V.:** Haber's Law is not actually a law because it is wrong sometimes, particularly at really short times and high concentrations, and then the factor should be a power function on the concentration which tends to drive the risks. With acute assessments in particular, the ten Berge

adjustment is appropriate to use. Consider putting “Haber’s Law” in quotations since it is not actually a law.

- **Susan:** In going through the background on the types of extrapolations where Haber’s Law adjustment can be applied, it discussed extrapolating from shorter exposure durations to longer exposure durations and vice versa. In Table 2, a different calculation was used. Is there a time when the scenario that was described for extrapolation from longer exposure to the shorter with an exponent of three is applied versus what is presented in Table 2, or is this because it is specifically subchronic to 24-hour acute adjustment that you adjust the days of the week?
  - **David:** Everything in Table 1 was a situation where the experimental study was looking at an exposure duration shorter than 24-hour and the team was extrapolating out to 24-hours. Everything in Table 2 is based on ATSDR’s intermediate minimal risk levels (MRLs) that are applied for up to a year, usually weeks or months, so in these cases, the only adjustment made was to take out the days per week component. The hourly adjustment from six hours to 24 hours per day still makes sense, but because they apply to a single 24-hour period, the extra adjustment for additional days of the week did not apply. It is ultimately still an application of Haber’s Law.
  - **Susan:** There are not examples in this case of extrapolating from a longer time period to a shorter time period.
  - **David:** There was one case when they applied that adjustment to hydrazine, and that is in Table 5.
- **John B.:** For chromium-3 water soluble compounds, the TRV was based on the ATSDR intermediate MRL. OEHHA has recent RELs for both acute and chronic, and the state used the OEHHA chronic RELs, but for the acute, the state used the ATSDR intermediate MRL instead of the OEHHA acute RELs. Why?
  - **David:** The team will look into this question and be ready to answer this question during the next meeting.

## Next Steps

Holly reminded the ATSAC members that the team shared a Word Document version of Document #3 with them, so they can type their notes in that document and be prepared for the upcoming discussion questions. The team requested that the ATSAC members send a final version of their notes in that document after this series of meetings and discussions has been completed. The team will compile and organize the feedback received from ATSAC members and post that online.

Holly thanked the ATSAC members for their time and the thoughtful discussion and feedback. Ben thanked everyone for participating and adjourned the meeting.

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## *ATSAC Meeting #6: February 11, 2025, 11:30am-2:30 pm PT*

Ben welcomed the ATSAC members and reminded the group of the Zoom webinar protocols. The focus of this meeting was to continue the ATSAC discussion questions, continuing the conversation from the previous meeting.

## ATSAC Discussion

### Questions on Document 4

Holly shared that the group discussed the first question on Document 4 during the previous meeting and invited ATSAC members to share any additional thoughts and noted that the DEQ-OHA team had follow-up from John Budroe's question on chromium-3 water soluble compounds to share with the group.

#### **1. What feedback or concerns do you have about the way DEQ proposes to adjust acute TRVs for exposure time in many cases (Section 2)?**

- **David:** During the previous meeting, John B. had asked why the DEQ-OHA team had based their TRV off of the ATSDR value instead of the OEHHHA value when the OEHHHA value was recently published in 2022. Dave shared that the ATSDR value was selected because even though the OEHHHA value was more recently published, it was based on a study from 1979, whereas the ATSDR value was based on a study from 1999, so the underlying science for the ATSDR value was more recent. The other reason was because if they selected the OEHHHA value and applied the ten Berge adjustment to Haber's Law to extrapolate that timeframe to a 24-hour exposure, then this acute TRV would be lower than the chronic value for the same compound.
  - **John B.:** There are times when an older study can still be a more appropriate study for the situation, so that is not always the main issue. The main reason why this caught John's attention was due to the fact that the team used an intermediate subchronic study rather than an acute study, because usually it is preferential to derive from an acute value and not a subchronic value. However, John also did the derivation calculation and also found that the final acute number was lower than the chronic number, which is problematic, so agreed with the final decision.
  - **John V.:** How often does OEHHHA use a value of six for the animal-human uncertainty factor instead of a three or a ten?
  - **John B.:** Not sure how often it gets used. For the older acute RELs, that uncertainty factor was not available.
  - **John B.:** For the interspecies uncertainty factor, it is likely going to be common to see the factor of six used more and more.
  - **Daisy:** Agreed with the use of the ATSDR value for different reasons. The OEHHHA study was acute, but the exposure time was only 30 minutes. The ATSDR study was not acute, but it was based on a port of entry effect. It seems less uncertain to derive the value from a port of entry effect study than to extrapolate from a 30-minute exposure to a 24-hour exposure.

#### **2. Are there any specific toxic air contaminants in section 2 to which Haber's Law should not be applied to adjust exposure time?**

- **John V.:** In Table 1, is it correct that an exponent of one was used in every case?
  - **David:** There is also a 1.33 and a 1.5 exponent, though in almost all cases they used one.
- **John V.:** For Table 2, where did the team start from to apply the exposure durations? How did the team handle different exposure durations for the calculations?

- **David:** Did not adjust exposure duration down to 24 hours. Usually, almost always, was starting from the ATSDR intermediate MRL, and the only adjustment made was to take out the intermittent component or the days per week adjustment, and did not apply any other adjustment. When ATSDR does their acute MRLs, they often use studies that are at or close to a two-week exposure duration, and they do not adjust down to 24 hours. Instead of taking out the intermittent time adjustment, another way to approach this would be to calculate the total hours and then extrapolate from that total number of hours down to 24-hours.
- **John V.:** Think that the current approach is better than the alternative David described because it is probably more health-protective than to try to adjust for the total duration of exposure.
- **David:** The team listed the exposure duration in the document for information, but did not actually make any adjustments based on that exposure duration in Table 2. Can make that clearer in the documentation.
- **John V.:** Agree that the approach is right but that the language could be clearer.
- **John S.:** To clarify, the team did take the daily exposure and adjust that to 24-hours, correct?
- **David:** Yes, those adjustments were included.
- **John S.:** Has there been any consideration of qualitatively describing where the team thinks these values tend to end up with this adjustment (e.g., that they are more health protective)?
- **John. V.:** Another way to do that would be to include an example, and that could be useful to show for one of these cases.
- **Daisy:** It is conventional for most agencies to adjust the hourly exposure and then the days per week. The approach taken by the DEQ-OHA team of removing the days per week adjustment is logical. Have never seen anyone take the approach of using Haber's Law to adjust the total exposure.
- **Daisy:** Provided the following comments on Table 1:
  - The exponent "n" is only valid if the value was derived within the 24-hour period. Based on experience, you cannot use the Exponent "n" to extrapolate beyond the data point range. It is important to check the original study and if it did not cover 24-hours, it is best to use the default n=1. You cannot extrapolate beyond the exposure duration that hasn't been tested.
  - There are some places where the POD = 1-hour REL, but that is conceptually not correct. It is better to use their POD and then apply whatever uncertainty factor you have.
  - For unit conversions, it is better to put the molecular weight divided by 24.45 so that people can calculate and if you copy the molecular weight wrong it is clearer.
  - Another suggestion is standardization of the format for the next time these materials are updated. Use the POD to convert it to the concentration unit immediately. This way it is more straightforward to see the human TRV compared to the animal study.
  - For the DAF, recommend being consistent throughout and specifying what the DAF is (e.g., RDDR or RGDR).

- For heptane, TCEQ extrapolated from 30-minute to 1-hour for their 1-hour ReV, but on page 5 the rule for POD stated “In cases where the source agency had already expanded an exposure shorter than 1 hour to 1 hour, DEQ used the 1-hour REL or ReV as the POD and made  $T_1$  equal to 1”, expecting to use  $POD_{adj}=1472.5$  ppm,  $T_1 = 1$  hour for the calculation based on this rule, yet  $POD=2945$  ppm,  $T_1=0.5$  ppm was used in the calculation. Just want to point out the inconsistency in following the rule in your calculation. For the unit conversion on heptane, the team did not give it the final value. They listed the molecular weight divided by the normal volume of the ideal gas.
- If the unit conversion is not necessary because the study unit is the concentration, recommend the team removes because they do not need to use it.
- **Daisy:** Provided the following comments on Table 2:
  - Overall, agree with this approach. Most agencies, when they use subchronic values, always use two duration adjustment effects, one for the hours and one for the days per week. It makes sense to use this approach when using intermediate or subchronic values from ATSDR to calculate acute TRVs.
  - Suggested incorporating comments that ATSAC members provided during the previous meeting to include the number of significant digits, since these are values that the DEQ-OHA team calculated.
  - Provided comments on terminology. The equation for the proposed acute TRV includes “subchronic TRV” in the formula; however, TRV is a DEQ definition, so it would be more accurate to state “subchronic reference value” since these values are coming from other sources (e.g., ATSDR, OEHHA, TCEQ). The formula and the table also include “days/week,” but this is also not correct because it is an adjustment factor. The true value is the days per week in the animal study divided by the days per week in the human study, so it would be better to state “days per week adjustment.”
- **John V.:** Also provided comments about terminology. The PPRTVs should have a sub-chronic p-RfC. The RfC is specific to the IRIS program, not to the PPRTVs.
  - **John V.:** For diethylene glycol monobutyl ether, it states that the source of the original value is the “2009 PPRTV subchronic REL,” but this should state that it should be the subchronic provisional RfC.
  - **David:** That is a typo. That should be an RfC not a PPRTV.
  - **John V.:** For Ethylene glycol monomethyl ether acetate, it just says “2011 PPRTV.” Recognizing that these are links to the original documents, the consistency in terminology throughout the document could be improved and it would be helpful to be as clear as possible.
- **Susan:** In the workbooks, information on the endpoints that were used for point of departure for each chemical seem to be split across multiple columns (basis for point of departure and target organ) and it was not clear how consistently those were being used. Recommended making sure that it is clear for each data point what endpoint was used for that calculation.

**3. What feedback or concerns do you have about the cases where DEQ proposes to apply toxicity information from a better studied toxic air contaminant (TAC) to a lesser studied, structurally similar TAC (Section 3)?**

- **John V.:** The narratives are very helpful, it helps the reader follow the logic and understand the basis for decisions, which is appropriate.
- **John V.:** For crotonaldehyde, was confused and not able to trace this back through Workbook 2. Do not see TCEQ values listed in Workbook 2 and am unclear what DEQ's approach was.
  - **David:** The starting point for the chronic value for crotonaldehyde is the same as the starting point for acrolein. In the narrative, they are saying that they agreed with TCEQ's argument that acrolein is a good surrogate for crotonaldehyde. However, DEQ did not use TCEQ's value for acrolein, they used a different agency's value for acrolein, which is why they do not reference TCEQ in the workbook because they did not derive the value from their number, they just applied their logic.
  - **John V.:** Was confused why the TCEQ value was not listed in Workbook 2, because there are values from other agencies listed.
  - **David:** The DEQ-OHA team generally did not add TCEQ values to Workbook 2 unless that was the value they were proposing to use because it is not listed as an authoritative source.
  - **John V.:** The IRIS value in Workbook 2 is incorrect, looks like a typo.
  - **Holly:** The DEQ-OHA team will make the narrative clearer and check that the IRIS value is correct.
  - **John V.:** Agreed with the approach of using acrolein as a surrogate to derive the chronic value for crotonaldehyde. Also agreed with the approach of using the brominated analogues from PCBs for PBBs and PBDDs, which the ATSAC had previously commented on.
  - **Holly:** The DEQ-OHA team had compiled the ATSAC members' feedback provided via email on this topic and provided a [link to this document](#).
- **Daisy:** Agree with the approach. Are all the chemicals in Document 4 also in Workbook 2?
  - **David:** Yes, all the chemicals are in Workbook 2, but the criteria for chemicals to appear in the colored tabs is that they must have a change from the previous TRV and have multiple options to choose from. If the chemicals do not meet both those criteria, then they would show up in the gray Appendix tabs.
- **Daisy:** Found one error in this section. TCEQ's chronic ReV for acrolein is not 8.1, it is 2.7.
  - **Holly:** The team will check this value.
- **John B.:** Had one comment on n-propylbenzene. In the narrative supporting information, it states that DEQ proposes to use all TRVs proposed for ethyl benzene to n-propylbenzene, but it does not include information on which endpoints are being used and which agencies' values are being referenced. It would be helpful to add the sources for each DEQ Proposed TRV Value (cancer, acute, and chronic).
  - **Holly:** The team will add that information.
- **John S.:** Agreed with the approach.
- **Susan:** Agreed with the approach and did not have any concerns about the groupings discussed in the table.

#### 4. What feedback or concerns do you have about cases where DEQ proposes to modify TRVs by changing uncertainty factors (Section 4)?

- **John V.:** There seems to be a surgical approach to identifying other states that are not listed as authoritative sources (e.g., TCEQ, New Jersey, Minnesota). Is there a discussion anywhere or can the team provide some background on how the authoritative and non-authoritative sources fit in?
  - **Holly:** The authoritative sources are in Oregon administrative rule; these are the sources that have been reviewed and put in the TRV tool. After ATSAC Meeting #2, the DEQ-OHA team heard feedback from the ATSAC members that it would be helpful in cases where they do not have information from the authoritative sources to look at other agencies that might have developed a value. In their updates document after that meeting, they described their approach that they would look at some of these other state agencies such as TCEQ in cases where no other authoritative sources had information. The DEQ-OHA team also developed a shortlist of chemicals that Oregon was particularly interested in due to exposure or potential for health hazards, and they had their contractor Eastern Research Group (ERG) look for toxicity values that have been developed by other organizations internationally and on the federal and state level.
  - **John V.:** Does the rulemaking allow for additions outside of the authoritative sources? Also want to understand the scope of how the team looked at other sources, as it seems like it was not a national, exhaustive evaluation.
  - **David:** For the subset of chemicals that ERG searched for (PFAS chemicals plus the methylnaphthalenes were the main ones), they looked at all 50 states as well as some international sources including Australia, the European Union, and Canada. For that subset of chemicals, that was comprehensive. These results are described in [this memo prepared by ERG](#). For chemicals that were not on that list, the main agencies that the DEQ-OHA team would check were TCEQ and Minnesota Department of Health (MDOH) if none of the authoritative sources had a value.
  - **John V.:** It would be useful to provide this documentation and would be helpful to refer to ERG's report. Adding more information would provide clarity and help the reader understand the broader context.
  - **Holly:** During the last rulemaking, one of the changes was adding DEQ in consultation with the ATSAC as an authoritative source, and that is how all of the values in Document 4 would fit into Oregon administrative rule.
  - **John V.:** When they went through this previous rulemaking process, did they receive much feedback in the public comment process about other states that should be considered authoritative sources?
  - **Holly:** Not sure if many public comments were received; that rulemaking was finished in 2021. TCEQ came up during ATSAC Meeting #2 in discussions, and after that point was included in the team's workflow.
- **Daisy:** Agreed with John V. that the team's approach could be described in more detail in the introduction. For example, explain that the ATSDR intermediate MRL was used because they could not find a chronic value.
- **Daisy:** Agree with the logic and approach to try to unify and confirm the other agencies' default uncertainty factors when using their PODs. For n-Hexane, it states that the TCEQ uncertainty factor is two and that DEQ changed this to three, which resulted in a change in the total uncertainty factor

from 180 to 300. Calculated that if the LOAEL UF was changed from two to three, the result should be 270 rather than 300. Also, stated that the proposed acute TRV equals the LOAEL divided by the UF. In this case, the LOAEL is not a correct term. In the original document, they calculated an HEC. Even though the value is the same and it is still 1,000ppm, the concept is different, because a LOAEL implies no HEC, so it might be better to use POD or HEC. Using the term LOAEL gives the wrong impression, like the raw POD was used without any adjustment, but in the original TCEQ document, they calculated the HEC and divided by the uncertainty factor of three for the interspecies.

- **David:** For that uncertainty factor, it does calculate to 270 but rounded to 300. Need to make that explicit.
- **Daisy:** Tend not to round the uncertainty factor. Here, the database uncertainty factor of three is not a half log, it is just three. Any approach is fine, but it is important to be consistent.
- **John S.:** Agree that for n-hexane it should be written as a LOAEL<sub>HEC</sub> before the uncertainty factors or a POD<sub>HEC</sub>.
- **John S.:** Looking at the narrative for acetone, for EPA, the standard for a LOAEL to NOAEL uncertainty factor is ten, not three.
  - **David:** ATSDR and IRIS will sometimes have a three if the effect is small or if they have a reason to think they are not that far from a NOAEL. ATSDR calls it a minimal LOAEL.
  - **John S.:** For EPA, it is a full ten, so that is not all authoritative sources. For EPA to use a minimal LOAEL requires a lot of documentation.
  - **Daisy:** CA DPR also uses a default of ten unless they have a very good reason to reduce it to three.
  - **John B.:** For OEHHA, they use one for a NOAEL or ten for a LOAEL for chronic RELs. For acute RELs, they use six if it is a mild effect for ten if it is a severe effect with a LOAEL.
- **David:** Would the ATSAC members recommend making a change the NOAEL uncertainty factor from two to ten?
  - **John S.:** Yes, because using a two would not be consistent with EPA's approach in developing a chronic value.
  - **John B.:** Agreed, would go with the ten.
  - **John V.:** Agreed.
  - **Susan:** Agreed.
  - **Daisy:** Suggested looking at the TCEQ study if they are relying on TCEQ to do the analysis. Most agencies default to ten, so if they used two, there is likely a reason.
  - **John V.:** TCEQ provided their rationale for using a UF<sub>L</sub> of two on page 23 of the linked document.
- **David:** Walked through the TCEQ document for acetone. TCEQ's description of the critical effect was neurotoxicity. The argument they used was not saying the effect was not severe, but rather that if they divide the LOAEL by two, then it puts the exposure concentration in a range that has not been associated with these kinds of symptoms, presumably based on other studies. Do the ATSAC members think this is a good justification for using a number other than ten for the uncertainty factor? The DEQ-OHA team would propose a three instead of a two, but asked if the ATSAC thinks it should be a ten in this case.



- **Daisy:** Agree with using a three. It is a human study, not an animal study. Even with an uncertainty factor of two, the concentration is less than 250ppm, which is not associated with increased symptomology, so it is the same symptoms as the LOAEL. TCEQ's value is already protective, and using a three would be even lower than that. Thought this reasoning was justified.
- **John B.:** Would go with a ten. Do not think the TCEQ justification is sufficient. In the OEHHA non-cancer guidelines, if it is a chronic value, they always use ten.
- **John S.:** EPA has a one or a ten. If the team wants to keep the value as a two or three, the rationale cannot cite all authoritative sources because EPA does not apply NOAEL to LOAEL that way. It is subjective symptomology.
- **John V.:** Would be more comfortable with a ten.
- **Susan:** Would be comfortable with a ten.
- **David:** Walked through the TCEQ document for n-hexane. The critical effect in mice for the 24-hour REV for n-hexane was developmental effects, a change in fetal weight.
  - **John S.:** The application of a three for this specific UF is not what EPA would do. They do not do adjustments from a LOAEL to a NOAEL. Whatever choice is made is fine, but the broader point of both examples is making sure the language is accurate.
  - **John B.:** If OEHHA was doing this, probably would not use a database uncertainty factor. For an acute REL, they would use a six for a mild effect or a ten for a severe effect, so the question would be whether you consider the reduction in fetal body weight to be a mild or a severe effect. Would not go with less than a six in that case and could definitely be argued into a ten. Would probably put the database at one given that they have a couple of reproductive developmental studies.
  - **John V.:** Since there are several studies, including a two-generation study and multiple species for inhalation, so they have the right route of exposure. Not sure why they used a three for the database uncertainty factor.
  - **John S.:** Could agree with the database uncertainty factor of one.
  - **John V.:** The UF for human variability (intraspecies) would be ten, the UF for interspecies of three makes sense because they are doing a dosimetric adjustment, then a UF of ten for the extrapolation from LOAEL to NOAEL, and a UF of one for the incomplete database. The total uncertainty factor would be 300 (10 x 3 x 10 x 1).
  - **Daisy:** Any way is fine, DEQ just needs to define their approach and rationale in the description. The value does not change much, the outcome is very similar. They can think about how to be more consistent.
  - **David:** Recapped feedback heard from the ATSAC: Moving the LOAEL to NOAEL adjustment factor to ten is consistent between the two cases at least. The other change in this case would be that the two-generation study means that you do not need the database uncertainty factor.

##### **5. Do you have feedback or concerns about cases where DEQ proposes to derive TRVs by making other types of modifications to values developed by other agencies (Section 5)?**

Holly and Dave shared that Section 5 is a miscellaneous section that includes all the adjustments that did not fit in the other categories.

- **Daisy:** For boron trichloride, agreed with the calculations. Suggested adjusting the way that the equation is written so that the final value is at the end and not the beginning.
- **Daisy:** For hydrazine, do not think that the duration adjustment is needed because they are using a short term, subchronic study to derive an acute value. In the workbook, the DAF is not an RGDR; they only adjusted for the inhalation rate. The study is from 1996, and the methodology is different from the recent RFC methods. They calculated the minute of ventilation divided by the body weight, which is called the inhalation rate. They did not do the RGDR, which is for a port of entry effect as well as a systemic effect. It is a regional dose, and the normalization factor is a surface area. Instead of calling it an “RGDR” in the workbook, recommend calling it a “breathing rate.”
  - **John V.:** It would be useful to add the full equation here as in other examples to that it is as clear possible what was calculated.
  - **David:** The formula used was referenced; it was Equation 4 from Section 2. However, if they do not apply the weekly adjustment, then hydrazine would not need to be included in Document 4 and the workbook because they would be using ATSDR’s exact value.
  - **Daisy:** The team could add hydrazine to the duration adjustment section (Section 2). Conceptually it is different from ATSDR because they are adjusting for the days per week, but because the number of days per week are the same (seven and seven), it equals one and does not change the value. Recommend taking this approach because technically the ATSDR is a short-term or intermediate value, not an acute value.
  - **John V.:** Agreed with that approach because it is more health protective.
  - **John B.:** Agreed.
  - **Susan:** Agreed with this approach and moving it to Table 2 so it is clear that duration was considered.
  - **John S.:** Agreed.

**6. Do you have any feedback or concerns about DEQ using the list of relative potency factors (RPFs) provided by the Minnesota Department of Health (MDH) for carcinogenic PAHs (using the 2017 IRIS IUR for benzo[a]pyrene as the index) (Section 5 table 6)?**

- **John V.:** Recommend adding benzo[a]pyrene to Table 5 with an RPF of one so it is clear that it is the basis for the other chemicals listed in the table and note that it is the index chemical.
- **Daisy:** Asked clarifying questions about the comments provided in the DEQ Notes column of Table 6 (Some of the rows in Table 6 of Document 4 include this statement in the “DEQ Notes” column: “TRV updated from 2018 value because old value used the same RPF but applied it to the outdated OEHHA IUR for benzo[a]pyrene rather than the newer 2017 IRIS IUR value”). Is the RPF the same as DEQ’s 2018 value? If not, where is it from?
  - **David:** Yes, the same RPF as DEQ’s 2018 value. There is not a proposed change to the RPF. The proposed change is to apply that RPF to the newer 2017 IRIS IUR value for the index chemical benzo[a]pyrene instead of OEHHA’s value for benzo[a]pyrene.
  - **Daisy:** The table is confusing in the way it is written because the RPF is not new, but the other column says that MDH adopted OEHHA’s RPF which gives the impression that there is a new RPF.

- **David:** MDH's adoption of OEHHA's RPF is not a new situation since they adopted it a long time ago.
- **Daisy:** That is what is giving the impression of a new RPF and slope effect, which is confusing.
- **David:** PAHs are a mixture of similar chemicals that have the same mode of action in carcinogenicity and their toxicity is all relative to an index chemical (benzo[a]pyrene). The DEQ-OHA is proposing to continue using IRIS's 2017 IUR for benzo[a]pyrene, and they are proposing to use the RPFs from the [MDH guidance document](#) and apply those RPFs to the 2017 IRIS IUR for benzo[a]pyrene.
- **Susan:** Since the RPFs did not change but DEQ is using a new source now, what source was DEQ using previously?
- **David:** The chemicals in Table 5 that have the comment in the DEQ Notes column, what changed was that in 2018 they adopted OEHHA's IURs for those PAHs inadvertently. They are now proposing to apply the same RPFs that California and Minnesota are using and apply that to the newer 2017 IRIS IUR for benzo[a]pyrene instead of the older OEHHA IUR for benzo[a]pyrene. The DEQ-OHA team is making sure that the RPHs are all applied to the same value for the same index chemical.
- **Ben:** Asked whether the ATSAC members agreed with the overall approach taken by the DEQ-OHA team for PAHs.
  - **John V.:** Yes.
  - **John B.:** Yes.
  - **Daisy:** Yes.
  - **Susan:** Yes.
  - **John S.:** Yes.

**7. Do you have feedback or concerns about any of the TRVs that DEQ is proposing to adopt without modification from non-authoritative (i.e., not EPA, ATSDR, or CalEPA) sources (Section 6, Table 7)?**

David shared that any TRVs that do not come from EPA, ATSDR, or CalEPA, the authoritative source must be DEQ in consultation with the ATSAC. When the DEQ-OHA team was looking at other sources (e.g., TCEQ and MDH), in the cases the ATSAC has reviewed thus far in the document, they modified the TRVs from other sources in some ways to make it a better fit for Oregon. In these cases, the TRVs came from other non-authoritative sources and the team is proposing to adopt as presented by the other sources.

- **John B.:** Were any TRVs adopted from international sources such as EU countries?
  - **Dave:** No, there were some values that ERG found in their review from Health Canada or the EU, but between the options that were available, the options that the DEQ-OHA team chose had the most documentation or met with their criteria the best. One of the criteria was that the derivation information was public and transparent. One reason that TCEQ is referenced frequently is that they do a good job of documentation, so it is clear and easy to see how they calculated the derivations. The team also wanted TRVs that were not derived from occupational exposure limits directly or that are derived based on an LC50 or an LD50. The ones that were left were true de novo derivations from a comprehensive literature review and traditional point of departure.

- **Daisy:** It could be helpful to add more description here in this section, so the reader has more information on ERG's review and the selection criteria. Consider expanding on the justification provided on why DEQ considered these of "adequate derivation quality" so there is more clarity on why these sources were selected.
- **Daisy:** Some chemicals have two different sources for the chronic and acute TRVs. Is that because the sources did not have a value for both?
  - **David:** Yes, in many cases that happened, where an agency had an acute and not a chronic value or vice versa.
- **John V.:** For lead, the way the process works for the National Ambient Air Quality Standards (NAAQS) for lead is a quarterly average across three years, and the reason it is a long-term average and not an acute value is because of the nature of the health effects, which tend to be neurological. The NAAQS is based on a significant database and is focused on an adequate margin of safety in the Clean Air Act, whereas the air toxics are based on an ample margin of safety to reflect the greater uncertainty and nature of the health outcomes. Is there a need for an acute value for lead?
  - **David:** It is conservative and health protective because the NAAQS value is designed for three-month rolling average, and they are applying it to a 24-hour period. Oregon does have a fair number of facilities with nearby residents. The NAAQS are meant to apply to a whole airshed as opposed to a concentrated area next to a source. One reason the DEQ-OHA team intends to have this as an acute value is to have that protection for people who are living very near to a source of lead, and because they are applying it in an acute scenario, it is health protective for those residents.
  - **John V.:** That sounds very appropriate for air toxics which tend to be more locally focused, and place based.
- **John V.:** For manganese, does the [2024 DEQ Manganese Memo](#) derive only an acute value or also a chronic value? Is the chronic value located somewhere else?
  - **David:** That document is from ATSAC Meeting #3 when the ATSAC had a whole meeting dedicated to discussing manganese. That memo is the formal writeup following those conversations. It is for the acute TRV for manganese.
  - **Holly:** This was following the petition on the acute TRV for manganese. The memo was the final compilation following the framing document and email exchanges with the ATSAC.
  - **David:** They do have a chronic value for manganese and the reason that value is not in this document is because they are using a chronic value from an authoritative source without modifications. No other source had an acute value, so the team had to derive one which the ATSAC assisted with during that meeting.
- **Susan:** In the workbooks, are the links to the sources in this table also linked to in the workbook?
  - **David:** Yes. Whenever DEQ is listed as the authoritative source in the workbooks, the team references Document 4 because that is where the modifications are discussed, but the link goes to the original source that the point of departure came from.
  - **Susan:** Having those links in the workbook as well as Document 4 is helpful.

**8. Pending DEQ and OHA consideration of ATSAC comments in previous discussion questions, do you agree with the TRVs where DEQ (in consultation with ATSAC) is the proposed authoritative source?**

Holly and David shared that the intent behind this question is to hear any final thoughts on the process and work put forward in this document. It is especially critical for these TRVs where DEQ in consultation with ATSAC is the authoritative source to hear affirmation from the ATSAC members to move forward with these proposed values.

Ben initiated a roundtable asking ATSAC members to affirm that pending incorporation of the guidance that the ATSAC members have provided they are confident moving forward with these values with DEQ in consultation with ATSAC as the authoritative source.

- **Daisy:** Yes.
- **Susan:** Yes.
- **John V.:** Yes.
- **John B.:** Yes.
- **John S.:** Yes.

**9. What feedback do you have related to the Proposed TRVs where DEQ is the Authoritative Source document?**

- **Daisy:** It could be helpful to make a table with the default settings for the different authoritative sources (EPA, OEHHA, ATSDR, and DEQ), like the one on the last page of the [Manganese Framing Document](#). This could be helpful for the future to reference to this table to see the defaults from the main sources.
- **John V.:** Why is the authoritative source “DEQ in consultation with ATSAC” and not DEQ and OHA?
  - **J.R.:** It is because the rule is housed in the Department of Environmental Quality. All of these standards are used in DEQ. The rules specify an interagency collaboration, and the team includes staff from both DEQ and OHA, with Holly and David providing outstanding effort.

## Next Steps

Holly reminded the group of the next meeting date and that the team is hoping to receive the final written answers from the ATSAC members following the third and final meetings in this series.

Holly, David, and J.R. thanked the ATSAC members for their time and contributions and Ben adjourned the meeting.

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### *ATSAC Meeting #7: February 19, 2025, 11:00am-2:00 pm PT*

Ben welcomed the ATSAC members and reminded the group of the Zoom webinar protocols. The focus of this meeting was to continue the ATSAC discussion questions, continuing the conversation from the previous meeting.

## ATSAC Discussion

### Questions on Document 5

#### ***Section 2: Chemical Groups that Can be Summed and Compared Directly to a TRV that Applies to the Group***

**1. Do you have any feedback or concerns about how we plan to organize groups of chemicals and how we plan to account for their toxicity?**

**2. Do you agree that these are the right compounds within each group?**

- **Susan:** Does Oregon DEQ-OHA have their own process for grouping chemicals by similarity (e.g., applying OECD guidance or defining similarity in a read-across), or is DEQ-OHA relying on groupings that have been proposed by authoritative sources?
  - **David:** The latter is correct. The DEQ-OHA has not developed their own criteria for groupings; all of the proposals are similar to how other authoritative sources group compounds. OEHHA has a lot of explicit information about how they group compounds, so in most cases the DEQ-OHA team followed OEHHA's groupings.
- **Susan:** Did not have any concerns about the groupings.
- **John V.:** Did not have any issues with the groupings.
- **John V.:** Was there a reason not to include the PFAS and PFOA compounds in this section?
  - **David:** The focus of this document is cases where the grouping has an effect on TRV application. PFAS is a class of chemicals, but right now, the DEQ-OHA team is proposing that each member of that group has its own TRV; they have not found a way to apply a single TRV to all PFAS or a relative potency factor approach for PFAS.
- **John B.:** Being very familiar with trimethylbenzenes, the RELs would have been very similar looking at them by each chemical and in actual use will be looking at mixed isomers, so is in complete agreement with this grouping.
- **Daisy:** Agreed with the groupings.
- **John S.:** Agreed with the groupings. For trimethylbenzenes, EPA's assessment and reference value accounted for the same groups.
- **John B.:** In general, agree with the groupings. Looking at the information for toluene diisocyanates, the language in the "Difference in approach from existing rule" column could be updated to be more accurate. ATSDR does not distinguish between isomers, and neither does OEHHA. OEHHA has the same RELs for either isomer or for mixed isomer.

#### ***Section 3: Chemical Classes with Toxicity Equivalency Factors or Relative Potency Factors***

**3. The World Health Organization (WHO) has a 2024 set of toxic equivalency factors (TEFs) for dioxins and furans. DEQ is currently proposing to keep using the 2010 EPA TEFs as applied by OEHHA. No other jurisdictions have adopted the new WHO TEFs to DEQ's knowledge. Should DEQ continue to apply EPA's 2010 recommended TEFs as proposed or consider proposing the 2024 WHO TEFs instead (Section 3.1)?**

- **Daisy:** Would adopt the 2024 WHO TEFs. Read the article and think it reflects a more curated database and the use of Bayesian statistics, so scientifically is better than the other TEFs. If the DEQ-OHA team is concerned about whether other agencies adopted the new values, maybe they can contact EPA or OEHHA to see whether or when they adopted these values.
- **John V.:** It was not clear that the rationale is very strong to say that it has not been adopted by others. The manuscript was well done and thoughtful. They did a comparison of the former 2005 WHO values and some of the values go up and some go down. The 2024 publication provides a strong science basis for using the WHO TEFs. They went through workshops, they did a systematic review, and they brought in Bayesian approaches.
- **John B.:** Would want someone with specific expertise in Bayesian statistics to take their own independent look at the manuscript. Would like another group to review this (e.g., EPA or OEHHA), or DEQ could put their own special purpose panel on this. Would like to see a review group to look at the manuscript and make sure that it is sufficient for use.
- **Susan:** Agree that the manuscript itself is really well put together and could create a wonderful new resource that pulls together a lot of information. Approaching the question from a process standpoint and thinking about how they have approach other data that have come in for consideration and leaned more towards John B.'s conclusion to at this point maintain using the EPA TEFs until this has been reviewed and adopted through an authoritative source. It also seemed that overall, the prior values might be more protective.
- **John S.:** Do not have an opinion one way or another. Do not know if this is part of a larger project of EPA adopting these values. It probably is worth taking a further look at its applicability.
- **Daisy:** Suggested contacting EPA or OEHHA to see how they stand because the manuscript was developed by someone at EPA and in terms of Bayesian statistics, they had experts participate in the panels. They broke into three panels during the 2022 meetings with different experts. Even for California DPR, they are moving towards incorporating Bayesian statistics in their risk assessment. It could be helpful to contact EPA or OEHHA to find out about their status in adopting the new TEFs. If they are in the process of adopting it then DEQ may want to adopt them; if they are not sure whether they will adopt them, then they might want to take a more conservative approach
- **John V.:** Know and have great confidence in many of the authors of the WHO paper. In the current atmosphere that EPA is working, they are not likely to get useful information in a timely way. However, there are a few people who are experts in the field who are available. For example, Linda Birnbaum is retired as the director of NIEHS, many of her studies were referenced in the WHO document, and she has done a number of different types of reviews. Oregon could pull together a group to review that approach, consider alternative approaches, and make recommendations.
  - **David:** The DEQ-OHA team could contact someone from EPA or other authors on the paper to see what their thoughts are.

#### ***Section 4: Inorganic TACs and their Associated Compounds***

**1. Do you have any feedback or concerns about how we plan to organize groups of chemicals and how we plan to account for their toxicity?**

## 2. Do you agree that these are the right compounds within each group?

### 4.1 Metals

- **John B.:** Might want to list the metals as “and inorganic compounds” rather than “and compounds.” What happens if you have an organometallic compound? Is that going to be substantially different from an inorganic metal compound?
  - **David:** In all of these cases, the “and compounds” are referring to inorganic compounds. They could be clearer about that.
- **Daisy:** Sometimes the DEQ-OHA team adopted groupings from ATSDR and sometimes they adopted groupings from OEHHA. In cases where there are different approaches from both ATSDR and OEHHA, how did the team decide which one to use?
  - **David:** Both ATSDR and OEHHA have sometimes changed their approaches, and the changes are most frequent between whether they separate or grouped the soluble and insoluble compounds together. Both agencies have shifted sometimes as they update their documents. The DEQ-OHA team followed a similar approach as selecting TRVS based on who had the more recent publication or the most recent studies, so they were case-by-case decisions.
  - **Daisy:** This could be clearer; they could add some more information on their rationale.
  - **David:** It is in the workbooks. For several of the acute values, they also made adjustments to an intermediate ATSDR MRL, and those are also in Document 4.
- **John V.:** Do not see organic mercury anywhere.
  - **David:** Was not able to find any inhalation toxicity values for organic mercury. That is the form that builds up in fish tissue. Not sure how common it is to find organic mercury compounds in air.
  - **John B.:** Never heard of an air risk assessment for hotspots in California that had any organic mercury issues.
- **John V.:** If the DEQ-OHA team changes each of these to specify that they are referring to just the inorganic compounds, are there organic forms that are also important as air toxics?
  - **David:** The TRVs that they have are based on studies with inorganic compounds. None of the inhalation TRVs they have for these groups of metals were done using organic forms of the compounds. So, part of the question is whether or not organic metals are emitted to the air, and do they have toxicity values that would be appropriate for inhalation of organic metals?
  - **Holly:** The team will do their homework before renaming these.
- **John S.:** EPA is taking a similar approach. On a mercury salts team, the assessment plan and literature review are posted on IRIS and that might be a good resource to figure out what studies are available regarding inhalation.
- **Susan:** No additional comments.

### 4.2 Non-Metal Inorganic or Ionic TACs

- **John B.:** Fine with the approach.
- **John V.:** Fluoride is very complicated. The proposal is reasonable.



- **Daisy:** Did not see sulfuryl fluoride on the list. Does Oregon have sulfuryl fluoride? It is a gas that is very poisonous and used for fumigation. Because of the ban of methyl bromide, a lot of fruits imported or exported use sulfuryl fluoride as a fumigant. Worked on a reference value for sulfuryl fluoride five years ago.
  - **Daisy:** Link to the [documents for sulfuryl fluoride](#).
  - **John B.:** It might not apply in Oregon. In California, sulfuryl fluoride for fumigation is under DPR's purview, but for spice or coffee fumigation, it becomes a hotspots use. It depends on the risk management structure in Oregon whether they will need to do a TRV for it or not.
  - **Daisy:** DPR is working on an air monitoring network to monitor pesticides in the air around the agricultural areas. They have screening levels similar to Oregon's TRVs and are working on updating them for 40 pesticides with new methodologies and new science.
  - **David:** Is the draft value for sulfuryl fluoride different enough in toxicity from the fluoride and compounds that this TRV would not be protective for sulfuryl fluoride?
  - **Daisy:** It is a risk assessment document; they reviewed the complete database. The value is finalized and has been reviewed internally and externally. The RfC is finalized, and they gave a range instead of a particular value.

## **Section 5: Silica**

**1. Do you have any feedback or concerns about how we plan to organize groups of chemicals and how we plan to account for their toxicity?**

**2. Do you agree that these are the right compounds within each group?**

- **Susan:** Support the approach taken for crystalline and non-crystalline forms and for the consideration of smaller sized crystalline particles of four microns or less for crystalline respirable forms.
- **John B.:** Good with the approach as outlined.
- **Daisy:** Agree with the two groupings.
- **John V.:** If you have a source that is emitting the crystalline form of silica that is larger than four microns, does that mean it is not covered by this TRV? What happens if there is a size range between four and ten microns that is still respirable?
  - **Holly:** The size fraction was really prominent that applied in the TCEQ document in that size range of under four microns.
  - **John V.:** Think it would be appropriate for it to just apply to respirable forms of silica and not have the four-micron cutoff.
  - **Susan:** As long as you are not considering particles that are smaller than ten microns, using ten microns as a cutoff.
  - **John B.:** The four-micron cutoff for crystalline silica goes back to the original studies and data that the OEHHA RELs and the TCEQ numbers are based on.
  - **David:** Is the recommendation from the ATSAC to make the silica TRV applicable to particles that are ten microns or less rather than four microns or less?
  - **John B.:** OEHHA went with the same cutoff as TCEQ.

- **John S.:** Wisconsin Health Services refer to crystalline silica as less than four microns for respirable. There might be some generic definition with inhalable versus respirable. Other places also have the cutoff at four microns.
- **Daisy:** A lot of people use a computational fluid dynamics model, and they do have a distribution difference between five or ten microns.
- **David:** There is a reason why PM2.5 is regulated more stringently than PM10 in the NAAQS. There is a difference between particles that are small enough to get all the way into alveoli compared to particles that are bigger and get stuck in the nose and bronchioles.
- **John S.:** [Jim Brown has a paper](#) with a definition of 50% penetration for thoracic as being ten microns and respirable fraction (unciliated airways) of being four. It is probably related to a definition.
- **John. V:** On Group 2, the size range is ten microns or less, so it is definitely worth looking into.

#### Questions on Document 6

**1. What feedback or concerns do you have related to the Proposed TRVs using PPRTV Values as the Authoritative Source document?**

**2. Is the science behind PPRTV screening values sufficiently robust to use for DEQ's air quality programs, including regulatory applications, when no other toxicity information is available?**

- **John V.:** What year were these PPRTVs done?
  - **Holly:** They started developing the screening PPRTVs in 2008.
  - **John V.:** The more recent ones were well done because of the way the peer review is done. Most of those were from 2010 and later, but if they are fairly recent, then they are well done in terms of the state of the science. These all have less certainty than the other values. In the TRVs, that is not reflected, correct?
  - **Holly:** That is correct, the list of TRVs is all on the same playing field.
  - **John V.:** In the very earliest days of the PPRTV program, had less confidence in those than in more recent years. The peer review process was much more robust in the later years than in the first years.
  - **John S.:** They have added more scrutiny and discussion around scientific issues. In more recent years they have increased that by adding systematic reviews, but it has been going on for quite a number of years since they restructured the review process.
  - **John V.:** Looking at the list of PPRTVs, every one of them is more recent than 2010, so comfortable with all of those on the list. Comfortable with the ones from 2007 and 2009 as well since they reflected the 2005 cancer guidelines. The ones there were issues with were not this set of chemicals.
  - **Daisy:** It is better to have a value than no value. It is better to have something than nothing and update it later.
- **John B.:** Good with the approach.
- **Susan:** Good with the approach. Could be helpful to flag high uncertainty values. There is no other value or data available for these and some of these values have been around for a while

and that has not changed. For the process moving forward and for values that have high uncertainty, is there a way to flag these so that if additional data became available it would be considered and to recognize that these screening PPRTVs might be serving as a placeholder until further data is available. There is a lot of information in this document about the uncertainty associated with these values, and not sure if that will be reflected as these TRVs move forward.

- **Holly:** The team will consider how to display the values and think about notes that go with them. These documents will move forward in the rulemaking process with the values in a supplemental document.
- **John V.:** The one chemical of this group that may warrant additional review is hexane because there is so much exposure to hexane through petrochemicals and gasoline, so it might be worth looking closely to see if there is any other authoritative source. That is a 2009 PPRTV which is okay, but it is surprising that there is not a better source to use.
  - **David:** A lot of authoritative sources have more solid values for non-cancer effects for hexane. It is just the cancer effects for which it is hard to find anything.

## Questions on Document 7

Holly reminded the group that the DEQ-OHA team checked every TRV authoritative source information with a cutoff date of August 8, 2024, and that included TRV information that was not yet finalized. On December 2, 2024, the team checked Table 1 in this document and updated the information for TRVs that had since become final. This document was circulated to the ATSAC on January 15, 2025. The team is aware that one of the values in this value from CalEPA for isoprene is now final, so there may be others. Most of the values in this table are from ATSDR. The DEQ-OHA team had to have a cutoff date for this meeting but moving forward they plan to closely monitor any updates that come out from authoritative sources, especially for chemicals on this list. They will evaluate any updates on a case-by-case basis and may consult with the ATSAC as any chemicals progress into draft or become final during this rulemaking process.

**1. Do you have any feedback or concerns about DEQ proposing to use the TRVs listed in this document (Table 1) that are not yet finalized by authoritative sources?**

**2. Would you propose an alternative in the case of any or all these toxic air contaminants?**

- **John V.:** It appears that the public comment period has closed for all of these. Are the public comments available? It might be useful to skim the public comments and see if there is anything particularly notable that could affect the development of ATSDR's values. Think it is reasonable to use these values because they typically do not change very much, although they can.
  - **Holly:** The DEQ-OHA team has not reviewed the public comments; they were tracking what stages they were at in the process. They will try to see what documents are available and take a look.
- **Daisy:** Recommended adding a column to the Excel workbook with the dates so that whenever they are finalized, they can update the dates. Did not have any concerns with using these values. Usually, these values have already been reviewed internally.
- **John B.:** In general, have no concerns with this approach. Had a clarifying question about the preferential use of ATSDR derived acute TRVs over OEHHA derived acute TRVs. Understand that

the basis for this preference is that OEHHA uses a 1-hour acute REL while the ATSDR is a 24-hour value. The exception to that rule is sensory irritation, because if OEHHA had a 1-hour and a 24-hour REL for a chemical like acrolein where the acute REL is based on sensory irritation, then the number would be the same. Assume that the preferentiality is in rule, has the team considered making that caveat?

- **David:** The rule is not that specific; the rule says what the authoritative sources are, and the team has been using internal guidance to select between them. There are cases when the team has deviated from the default algorithm to choose an OEHHA value over ATSDR.
- **John B.:** In the Proposed TRV Update and Selection Process for ATSAC Review document, it shows the order of authoritative scientific agencies for acute non-cancer TRVs. That order of preference is not set in stone?
- **David:** Correct, that order of preference is not in rule.
- **Holly:** The team also developed an updates document following ATSAC Meeting #2 and clarified that the order of preference would just be a screening step, and that they had a preferred list of TRV attributes that they would consider for each one. It was a case-by-case basis looking at each TRV and choosing which source best matched the attributes.
- **Daisy:** Assumed that when Oregon selected the acute TRV, they went to ATSDR first, and if they did not have an acute value, used OEHHA's value with a duration adjustment, and then used ATSDR's intermediate REL.
- **David:** The team did have an algorithm that they used to go through, but that algorithm is not in rule.
- **Daisy:** Used a tiered approach for values from authoritative sources that most closely matched Oregon's 24-hour acute value. This hierarchy is not clearly specified in Document 4. The arrangement in the document by section does appear to follow this hierarchy.

## General Questions

**1. Did you find any errors or have feedback or concerns about the content in any of the ATSAC review materials?**

**2. Do you have any feedback or concerns about a specific toxic air contaminant TRV that we have not discussed or flagged anywhere else?**

- **John B.:** Looking at Workbook 1, there is a column titled *Reason for Change*, and there are several entries that say, "More Recent Science," but it should be "More Recent Evaluation." While an agency may have done a more recent evaluation, there is not necessarily a substantial difference in risk assessment methodology or new data.
  - **David:** There is a distinction between when they say, "More Recent Science" and when they say, "More Recent Publication Date." "More Recent Science" means that the critical study that the value was based on is more recent, while "More Recent Publication" refers to the last time that an agency reviewed the data and made an update. It would be helpful to add a key for the different reasons for changes to describe what these notes mean in more detail.

- **John B.:** It would be helpful to add clarification on that.
- **Daisy:** It would be helpful to clearly define these terms.
- **Daisy:** For the three authoritative sources, their methodology is very similar, so there are not going to be inconsistencies. When there is not a value from any of the authoritative sources and they use values from other agencies such as TCEQ, there is deviation since they use different methodologies. For example, TCEQ adopted a different methodology for chemicals with an extra thoracic port of entry effect (DAF equals one instead of normalized by minute of ventilation divided by the surface area). Therefore, if a TCEQ value is adopted for a chemical with the port of entry effect, then it is inconsistent with other agencies. Did not see a case adopted from TCEQ with the port of entry effect. In the future, this could create an inconsistency in methodology.
- **Daisy:** In the worksheet, there were places where the power signs are linked together, and it is not clear that it is meant to be a power. It might be helpful to add a power sign in those cases. That could create errors in the future.
- **John V.:** What form of feedback does Oregon find most useful from the ATSAC members? Is it the written materials that members will provide subsequently or the verbal comments that the members have already provided, or a combination?
  - **Holly:** It will be a combination. The team will take the feedback that has been received and develop comprehensive meeting minutes and send those to the ATSAC members for review, and those will be an important resource during the rulemaking process. The written comments will also help the team have a final summary of where ATSAC members landed after hearing everyone's discussion. The combination of the meeting minutes and the final written summaries from ATSAC members will give the team a comprehensive picture to move through the rest of the rulemaking process.
  - **John V.:** Will the meeting minutes and the individual written comments be part of the public record?
  - **Holly:** Yes. The team will compile all the written comments and those will be posted online as well as the meeting minutes, so those will all be publicly available.
  - **John V.:** The Rules Advisory Committee (RAC) and Fiscal Advisory Committee (FAC) are subsequent steps in the process. Is there anything that the ATSAC members should be clear about in their comments to make that those committees have the information that they need for this process?
  - **J.R.:** There may be potential information submitted by members of the RAC. The RAC will include a broad swath of community members including members from industry, community, environmental advocates, and other agencies; the FAC will include the same members as the RAC. They anticipate that they might receive specific comments and toxicological information on some chemicals. If the team receives that information, they will review that and may bring that back with questions to the ATSAC members. The worksheets from the ATSAC members will give the team everything they need to bring to the RAC and the FAC. A bigger portion of the RAC meeting will be on how these TRVs fit into the policy and implementation of DEQ's program. There will be technical discussion, but most of that will probably come in writing.
  - **John V.:** Would be happy to help provide a response to anything that is needed in the future.

- **John V.:** From the beginning, have been very impressed by the amount of work that the team has put in, and hope that the comments that the ATSAC has provided will not be a barrier to moving forward.
  - **David:** In the written comments, categorizing comments by which things the team should fix now before the process moves on versus what ideas and improvements should be incorporated the next time, they complete a review would be very helpful.
- **Susan:** No additional comments and thanked the team for the materials that they put together.
- **John S.:** What is the timeframe for delivering the ATSAC members' final written comments?
  - **Holly:** The target date for receiving comments is Wednesday, March 5. The team will send an email with the dates to the ATSAC members and requested that ATSAC members let them know if more time is needed to complete the written comments.

## Next Steps

Holly shared that this meeting completes the current meeting series. Holly and J.R thanked the ATSAC members for their time and contributions to these meetings and shared that the DEQ-OHA team learned and benefited a lot from these discussions. The team would appreciate the ATSAC members' final written responses to the questions in Document 3 by end of day, Wednesday, March 5.

There is one specific question on 1-methylnaphthalene from state risk assessors that the team would like the ASTAC members to review and weigh in on. The team will share the email thread with the ATSAC members and asked that ATSAC members read through that and provide input in the next month.

The next ATSAC meeting will be scheduled and is anticipated to be held in May. This meeting will focus on diesel particulate matter (DPM). The ATSAC members will receive an email with instructions to access a file transfer site to provide access to some of the peer reviewed documents and materials for review.

**Appendix F: Meeting Minutes for  
ATSAC Meeting #8 on Diesel  
Particulate Matter**

# Air Toxics Science Advisory Committee (ATSAC)

Meeting 8: May 14, 2025, 10:00 am-11:15 am PT

## Meeting Minutes

### Meeting Attendees

| ATSAC Members          |                                                      |
|------------------------|------------------------------------------------------|
| John Budroe            | California Environmental Protection Agency (retired) |
| John Stanek            | Environmental Protection Agency (EPA)                |
| John Vandenberg        | Duke University                                      |
| Qiaoxiang (Daisy) Dong | California Environmental Protection Agency           |
| Susan Tilton           | Oregon State University                              |
| Project Team           |                                                      |
| Apollonia Goeckner     | Oregon Department of Environmental Quality (DEQ)     |
| Dana Crosby            | Oregon Health Authority (OHA)                        |
| David Farrer           | OHA                                                  |
| Holly Dixon            | OHA                                                  |
| J. R. Giska            | DEQ                                                  |
| Facilitation Team      |                                                      |
| Ben Duncan             | Kearns & West                                        |
| Angela Hessenius       | Kearns & West                                        |

Meeting slides can be found at <https://www.oregon.gov/deq/aq/Documents/ATSACM8slides.pdf>

### Welcome

**Ben Duncan, Kearns & West (K&W) facilitator**, reviewed the Zoom webinar protocols and facilitated introductions from the ATSAC members and DEQ-OHA project team.

**Holly Dixon, Oregon Health Authority (OHA)**, reviewed the meeting agenda, which included 1) Welcome, 2) ATSAC Discussion Period on Diesel Particulate Matter, and 3) Next Steps.

Holly reminded the ATSAC and attendees that all the ATSAC materials including the meeting recordings, meeting minutes, and compiled written responses from ATSAC members are publicly available on the [ATSAC website](#).

### ATSAC Discussion

In preparation for this discussion, the DEQ-OHA project team requested that ATSAC members review [ATSAC Document 8: DEQ's Proposal for the Diesel Particulate Matter Cancer Toxicity Reference Value Framing Document for DEQ's ATSAC](#). The ATSAC discussion followed the five discussion questions provided in ATSAC Document 8.



## 1. Do you see additional uncertainties with the proposed cancer TRV not already covered in the DPM Framing Document?

### Discussion:

- **John Vandenberg:** Found the framing document to be very well done. It was balanced, complete, and provided the information and resources necessary to be able to comment on the decisions that DEQ and OHA need to make. The [Ramboll Environ white paper \(2016\)](#) was not linked in the document, and that would be helpful to include. One additional uncertainty is that none of the cancer potency assessments reviewed in the DPM framing document fully consider age as a risk factor. The [supplement](#) to the [2005 EPA guidelines for carcinogen risk assessment](#) identifies the potential for additional risk to children due to a variety of biological and exposure differences with adults. Therefore, age-dependent adjustment factors have been applied for about the last 20 years by EPA and other organizations. Those factors are applied for chemicals that have evidence of a mutagenic or genotoxic type of mode of action, which is relevant for DPM, as IARC has commented. John V stated that he is not recommending that the agencies modify the proposed TRV, but rather he recommends that this uncertainty be more explicitly described in the documentation because none of the potency factors included have considered that. There were some calculations in the Vermeulen et al. 2014 paper that included from ages 5-80, so it covers part of that range but not the full range. The most important age range to cover would be from birth to six years. Recommended including a more extensive discussion about the specific concerns and quantitative aspect of children being exposed to diesel exhaust and DPM.
- **John Budroe:** Thought the DEQ-OHA did an excellent job in discussing everything including the uncertainties. One addition is that New Jersey Department of Environmental Protection (DEP) also adopted OEHHA's DPM IUR in the same way that Washington state did. Agreed with John V. to add a note about early life susceptibility. There are some differences in the way that US EPA and CalEPA approach age-dependent adjustment factors. CalEPA applies an early age adjustment factor to all carcinogens, not just the mutagenic or genotoxic carcinogens. OEHHA also does not adjust the potency factors, they adjust them after the fact in the site risk assessment part of the process.
  - **John B.:** Clarified that CalEPA's approach is carried out through the Hot Spots Program. In Hot Spots, age-dependent adjustment factors are applied to a risk assessment around a stationary source and is site-specific.
- **Susan Tilton:** Appreciated all the work that went into the framing document. Thought it did a good job of describing the underlying studies that went into the calculations and the uncertainty associated with those. One way to address uncertainty is through the Bradford-Hill criteria, which might be helpful to include.
- **Daisy Dong:** Thought that the framing document was very solid and all the information needed was there.
- **John Stanek:** Thought that the framing document was complete and well done. There are a few aspects of the uncertainty sections that could be a little more specific from the Ramboll paper and the full CalEPA writeup to add some clarity.
- **John Stanek:** Asked a clarifying question about the TRV in the DPM framing document.

- **Holly:** The framing document includes the proposed cancer TRV for DPM, which is  $0.0033 \mu\text{g}/\text{m}^3$  (which is adjusted for the one-in-one million risk). This DPM TRV comes from CalEPA's inhalation unit risk (IUR) for DPM, which is  $0.0003 (\mu\text{g}/\text{m}^3)^{-1}$ .

**2. It appears Ramboll Environ (see Table 1 of Ramboll Environ's white paper) calculated an inhalation unit risk (IUR) for Vermeulen et al. 2014 using an excess lifetime cancer risk of 17 per 10,000 at a DPM-proxy (Elemental Carbon) concentration of  $1 \mu\text{g}/\text{m}^3$  (see Table 2 of Vermeulen et al. 2014). What do you think about Ramboll's approach and DEQ's interpretation of where that IUR came from?**

*Questions 2 and 3 were asked together at the same time and ATSAC members answered and discussed them together. Responses to both questions are recorded under Question 3 below.*

**3. Is there another IUR from the Ramboll paper (or average of some or all of them) (Table 1 of Ramboll Environ's white paper) that you believe is more scientifically sound than CalEPA's IUR for DPM?**

Holly shared that these two questions were posed to get specific feedback and focus on some of the more recent studies that have been published since the CalEPA IUR value was developed.

#### **Discussion:**

- **John V.:** Table 2 of the Vermeulen et al. 2014 paper shows estimates of lifetime risk per 10,000 for the general public aged 5-80 years and also for workers exposed at ages from 20-65 years. The estimate for the general public is most appropriate to evaluate an average exposure of  $0.8 \mu\text{g}/\text{m}^3$ . The risk from age 5-80 is therefore 21 per 10,000. To calculate the risk for  $1 \mu\text{g}/\text{m}^3$ , you take 21 and divide it by one over 0.8, which equals 16.8 and rounds to 17. This is consistent with what the DEQ-OHA team did, and it was calculated correctly. However, that derivation does not include consideration of age-dependent adjustment factors for ages 0-2 and 2-6, as mentioned earlier. Although that paper was published after the 2005 guidelines, they did not apply age-dependent adjustment factors, which would be appropriate here.
- **John V.:** When you look across Table 1 from the Ramboll paper, some of the different authors or reports provided a range of IURs. EPA was a range in 2002 from  $10^{-3}$  to  $10^{-5}$ <sup>a</sup>, OEHHA was  $3 \times 10^{-4}$ , the Vermeulen paper was  $1.7 \times 10^{-3}$  and then was revised based upon comments from Dr. Kenny Crump about ways to do additional analyses with a lag period that came out at  $1.1 \times 10^{-3}$ . These values are all close together. It was useful to look at that table that they provided to see the different assessments that had been done.
- **John B.:** The interpretation of how Ramboll calculated their IUR from the Vermeulen data appears to be accurate, and it is interesting that the IUR that you get with or without the adjustments that Dr. Kenny Crump suggested still fall within the IUR range that OEHHA originally generated, so it is all within the same ballpark. There might be strengths associated with taking

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<sup>a</sup> DEQ-OHA Note for Context: EPA's 2002 assessment did not include an IUR that it recommended for use in DPM cancer risk assessments. As the [Ramboll white paper](#) states, "The US EPA chose to take a set of exploratory approaches to estimate the possible magnitude of cancer risk...This exploratory analysis concluded that environmental cancer risks from exposure to diesel exhaust were possibly in the range of  $10^{-5}$  to almost  $10^{-3}$ , while acknowledging numerous uncertainties and assumptions in reaching this conclusion." Currently, the EPA does not have a recommended IUR for DPM.

the Vermeulen paper and turning it into an IUR, but it would be a long, complicated project, and is not likely worth investing the resources in that process. The Vermeulen data is available, and OEHHA has not decided to reevaluate diesel exhaust for cancer risk since 1998 and is not likely to do that anytime soon.

- **Daisy:** Suggested taking the Ramboll paper and using the range they provided instead of using the OEHHA value. The reason is because OEHHA's TRV is based on an older study and has a lot of limitations. The Ramboll review includes more recent studies. For example, the Vermeulen et al. 2014 was the most recent study included in the Ramboll review, and the Vermeulen paper is a relatively new study compared to OEHHA's critical study. Recommended using the information in the Ramboll review because it is newer, HEI already reviewed these studies. As a whole, the Ramboll white paper represents the most recent literature review on this topic, so recommended DEQ-OHA use the Ramboll white paper and take the lower end of the IUR range to calculate the TRV. Eventually, EPA or OEHHA will likely reevaluate these studies. There is still some debate in the Vermeulen study, but compared to the OEHHA study, think the Vermeulen study did a good job. The older diesel exhaust composition is also very different from the contemporary composition, so that is another reason to use the newer study. Also, no other agency besides OEHHA thinks that study is adequate to develop a quantitative estimate, so that study apparently has a lot of limitations, but at the time it was the only study available. This newer study is better science compared to the older study and it is better to base it on a newer study and take a range. Think that Ramboll did a good job.
- **Susan:** Felt one of the primary conclusions from the Ramboll paper was that there is not a consensus on the analysis approach for handling these newer studies and especially the meta-analysis. Saw these studies in a similar way to John V. and John B., that they provided confidence for the CalEPA value since they all converge within a similar range, but not necessarily providing a rationale for choosing a separate estimate. It would be helpful to incorporate more information about these ranges that have been proposed and that are available into the framing document so that the information is there.
- **John S.:** Agreed with Susan's approach. Reproducing the table from the Ramboll paper in the framing document, perhaps in an appendix, would add confidence. Even though DEQ selected a single value, it is in the middle of all the other cancer estimates. Providing it in context somewhere would help strengthen the rationale.

#### **4. What other questions or concerns do you have related either to the proposed DPM cancer TRV or to the DPM Framing Document?**

*Questions 4 and 5 were asked together at the same time and ATSAC members answered and discussed them together. Responses to both questions are recorded under Question 5 below.*

#### **5. Do you agree with CalEPA's inhalation unit risk DEQ proposes to adopt to calculate a cancer TRV? If not, do you have an alternative suggestion?**

##### **Discussion:**

- **John V.:** No other questions or comments. Agreed with the selection of CalEPA's IUR that DEQ proposes to adopt for the TRV derivation for DPM. CalEPA products are considered authoritative

and using the OEHHA value would be consistent with using such assessments as the basis for TRV derivation.

- **John B.:** No additional thoughts or concerns regarding the framing document. Agreed with using CalEPA's IUR for DPM. The studies that it is based on are well described and well conducted. The IUR received multiple rounds of public comment and peer review and was revised in response to those received comments. US EPA has enough confidence that it uses it in the regional screening level tables for Superfund site risk assessment, and the states of Washington and New Jersey also use the OEHHA diesel exhaust IUR, so it would be perfectly appropriate for DEQ and OHA to use the OEHHA DPM IUR as the basis for a TRV.
- **Susan:** Agreed with John V. and John B. Recommended adding a description of the derivation of the TRV from CalEPA's IUR. It would be helpful to include that in the framing document.
- **Daisy:** Recommended using the Ramboll paper and picking the lower end of the range. This is a more thorough consideration of more recent studies and current science, which is more robust than the study that OEHHA's value is based on.
- **John S.:** Agreed with DEQ's proposal for the cancer value and did not have any other alternative suggestions. Suggested adding the context of where this proposed value falls compared to the other analyses and proposed ranges.

Holly asked the ATSAC members an additional question about nomenclature related to diesel exhaust versus DPM. These terms have different meanings and there are differences in how they are used in different documents over time. DPM is the fraction of particulate matter that is used in relation to the TRV that DEQ is using from CalEPA and the non-cancer value from EPA. Diesel exhaust is used in a lot of more recent literature and a lot of chemicals like polycyclic aromatic hydrocarbons (PAHs) are not just on particulate matter but are also in the vapor phase. DEQ is currently proposing to continue using DPM as the nomenclature for the TRV, and Holly asked if the ATSAC had any thoughts or suggestions related to this proposal.

#### **Discussion:**

- **John V.:** Diesel exhaust is a complex mixture of particles and gases, and yet it is important to have an indicator that can be evaluated straightforwardly, which in this case is DPM. There is some similarity between this approach with photochemical oxidants in which ozone is used as the indicator for a whole class of photochemical oxidants. Using DPM in the TRV derivation is exactly what the DEQ-OHA team should do, and perhaps some rationale for that could be added. Another aspect of this is that as new requirements have been put on diesel engines, the nature of the emissions have changed somewhat. The composition of diesel exhaust has changed over time, and it becomes very complicated to track that since large diesel engines can last a long time, so it makes sense to focus on DPM as an indicator that can be measured and used. With newer diesel engines, there is perhaps a more significant effect of ultrafine particles, which are not measured very well. Overall, using DPM as an indicator for diesel exhaust is very appropriate.
  - **John V.:** The typical measurement methods do not capture ultrafine particles quantitatively. There is a lot of uncertainty about the health outcomes which could be significant for ultrafine particles, but there are a lot of gaps in the knowledge base whereas DPM is a known entity.

- **John B.:** When the OEHHA IUR was developed, there was a realization that even if it were possible to filter 100% of the particulates out of diesel exhaust, then the risk from diesel exhaust would likely be underestimated since there would still be gas phase chemicals (e.g., benzene, acrolein). DPM is still the best metric that can be used.
- **Susan:** No additional comments. Appreciated that DEQ provided the definitions within the framing document.
- **Daisy:** Agreed that DPM makes sense to use.
- **John S.:** Agreed with using DPM.

**JR Giska, Oregon Department of Environmental Quality (DEQ),** asked another additional question about the newer technology diesel engines have a lower overall loaded of DPM and their exhaust emissions, but the DEQ-OHA team could not find any great studies on the compositional differences for the newer exhaust versus older exhaust and asked the ATSAC members if they had feedback on how the team might consider that for their TRV.

#### **Discussion:**

- **John B.:** Back around the time of the [Health Effects Institute \(HEI\) Advanced Collaborative Emissions Study \(ACES\)](#) study, there were studies that looked at the genotoxicity of both old and new diesel engines. By volume of diesel engine exhaust, the new technology engines were much lower genotoxicity because they generate a lot less particulate matter. However, normalizing to microgram of particulate, the new technology engines were more genotoxic than the older engines. Not aware of any recent studies but have a sense that at a minimum, the particulate from a genotoxic standpoint is going to be the same between both the old engines and the new engines.
- **John V.:** One of the challenges with the new diesel engines is that the emissions have changed so much and if it has a well-functioning particulate trap and condensers, then it becomes very difficult to study them. They cannot do any controlled human studies of diesel exhaust because they cannot get the concentrations correct. It is a challenge in terms of research and was not aware of any recent studies that would provide good insights on this, except for on the monitoring side which indicates that the composition has changed and likely continues to change.

JR asked an additional question of the ATSAC members. Currently, DEQ assesses DPM, PAH, and metal emissions separately, which leads to PAH driving risk because of the current TRVs. Given the complex mixture of diesel exhaust, is it appropriate to count PAHs and metals if they are also going to be assessing DPM for risk, even though the DPM itself may be composed of some of those components?

- **John B.:** If diesel exhaust emissions were quantified, then California would not require a double count of risk from PAHs and metals. They would not have expected someone to speculate the PAH and metal content and add that to the diesel exhaust cancer risk.
  - **John V.:** Asked for clarification from John B. about how PAH and metals risks are considered if they are present in DPM, i.e., it is not double counting to consider all components of DPM as being part of DPM risks, and separately to have PAH and metals risk assessments. **(DEQ and OHA further clarified this point with John Budroe after the meeting. See Appendix A.)**

Ben opened the discussion to any final thoughts from the ATSAC members.

- **John V.:** The DEQ-OHA project team has done an excellent job providing information that the ATSAC members needed. The succinct summary provided and pointing to where the data is coming from is very helpful in supporting the ATSAC's evaluation and providing comments.

## Next Steps

Holly reviewed next steps for the ATSAC members and thanked the ATSAC members for all the feedback they have provided to date which has been incredibly helpful. This meeting was the last scheduled meeting of the ATSAC on the TRV proposals. Holly requested that the ATSAC members submit their discussion question worksheets via email by May 28. The DEQ-OHA team will post all final materials to the ATSAC website and integrate the ATSAC feedback into the TRV proposals and documentation for the next rulemaking phase and will provide updates to the ATSAC for their awareness.

JR thanked the ATSAC members for their support, input, and time throughout the ATSAC process and reminded the ATSAC members of the next steps in the rulemaking process. The scientific review process is currently wrapping up and the next step in the process is to convene a rules and fiscal advisory committee. DEQ plans to convene these committees later this year, and those committees will be followed by a public hearing and public comment period. The DEQ-OHA team will review written comments received on the TRV proposal, and at that stage, they may reach out the ATSAC if there are any items they would like to solicit feedback from the ATSAC on via email or an ad hoc meeting if necessary. After reviewing the comments received, the final step of the process will be to present the proposed rules to the Oregon Environmental Quality Commission for consideration, which is anticipated to occur in 2026.

Holly outlined the criteria that the DEQ-OHA project team will use to determine when to seek additional feedback from the ATSAC during the rest of the rulemaking process that JR described. These criteria include if there is a new concept or process that comes up that had not previously been discussed with the ATSAC and that the team thinks is important to consult with the ATSAC on. Holly also shared that the team plans to send a short survey to the ATSAC members to solicit feedback on how to improve the ATSAC consultation process for the future.

John V. asked clarifying questions about whether the current ATSAC will be completed with the rest of this rulemaking process and if DEQ will convene a new ATSAC in the future during the next TRV review process and whether they would look for any of the current ATSAC members to continue through the next TRV review process. JR responded that the ATSAC members currently have three-year appointments in rule. The DEQ-OHA project team hopes that if there are any questions that fall outside of the three-year appointment timeframe for the current ATSAC members, that they would be open to answering those questions and DEQ could possibly extend that timeframe. DEQ would convene a new ATSAC for future rulemaking processes. JR also shared that they plan to consider language in the proposed rules to change the frequency of TRV review since the current requirement to complete the review process every three years feels too frequent.

John V. also commented that the work completed by the DEQ-OHA project team could be highly valued by other states. It might be useful to communicate with colleagues in other states and regions through larger state organizations or other forums about the process, analysis, and data that the team has put

together. It could be a useful model for other states to consider and could benefit from. Daisy echoed this comment and shared that the team did a great job consolidating all the values from different agencies and compiling the workbook which could be very useful for other states, especially since this work has already gone through quality assurance and quality control. Sharing this resource beyond Oregon could help to avoid redundant work by other states.

**David Farrer, OHA, JR,** and Holly shared thanks and appreciation for the ATSAC members for contributing their time, expertise, and input to support the ATSAC process.

Ben thanked everyone for participating and adjourned the meeting.

## Appendix A: Clarification email from John Budroe to OHA on June 25<sup>th</sup>, 2025.

*“California air districts would not require a Hot Spots risk assessment to speciate a diesel exhaust source into DPM + PAHs + metals. The cancer risk is considered to be associated with the total diesel exhaust (particulate + gas phase), with DPM being used as the surrogate metric. If a theoretical diesel exhaust source had a filter that removed 100% of the DPM from that source, then the calculated cancer risk from that source would be zero in a Hot Spots risk assessment (even though there would be a residual cancer risk from gas phase components like benzene). I agree with John Vandenberg that a diesel exhaust source risk assessment that includes PAH and metal speciation should not report:*

*DPM = 10 in a million*

*PAH = 1 in a million*

*Metals = 2 in a million,*

*and say the diesel exhaust cancer risk is  $10-1-2 = 7$  in a million. What I was trying to say was that the diesel exhaust source cancer risk in this case should be reported as 10/million, and not  $10 + 1 + 2 = 13$ /million, unless the Oregon site risk assessment rules are different from the Hot Spots rules and require exhaust speciation.”*

# **Appendix G: ATSAC Written Responses to DEQ and OHA Manganese Questions**





# ATSAC Compiled Worksheets- Manganese

## ATSAC Worksheet for 4-3-2024: Manganese Acute Exposure TRV Proposal Options

**Instructions for ATSAC Members:** If useful to you, you can fill out the green shaded portions of this worksheet before, during, and/or after the ATSAC meeting on 4-3-2024. You can send in this worksheet to DEQ after the meeting (email Apollonia Goeckner at [apollonia.goeckner@deq.oregon.gov](mailto:apollonia.goeckner@deq.oregon.gov)).

**Excerpt from page 6 of the [Manganese TRV Framing Document](#):** To aid ATSAC discussion, Table 4 outlines a range of potential proposals for DEQ's acute manganese TRV. Not all potential options are in this table. DEQ wants to hear from ATSAC members on the benefits and drawbacks of the proposals in Table 4. DEQ also wants to know if ATSAC members think a better proposal option is available other than those listed in Table 4. ATSAC member feedback will inform DEQ's final proposal.

**Table 4.** Potential options for DEQ's acute manganese TRV for ATSAC to discuss.

| TRV Proposal Name                                                          | TRV (ug/m <sup>3</sup> ) | Uncertainty Factor (UF) Information |                               |                       |                             |                          |           | Human Equivalent Concentration in TRV? | Time Adjustment in TRV? | DEQ Notes                                                                                                                          |
|----------------------------------------------------------------------------|--------------------------|-------------------------------------|-------------------------------|-----------------------|-----------------------------|--------------------------|-----------|----------------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------|
|                                                                            |                          | UF <sub>A</sub> Inter-species       | UF <sub>H</sub> Intra-species | UF <sub>L</sub> LOAEL | UF <sub>S</sub> Sub-chronic | UF <sub>D</sub> Database | Total UF* |                                        |                         |                                                                                                                                    |
| <b>Option 1</b><br>TCEQ                                                    | 5.0                      | 3                                   | 10                            | 2                     | NA                          | 6                        | 300       | No                                     | No                      | No changes to TCEQ's 2017 final acute Mn TRV. This includes TCEQ's policy that 300 is the maximum total UF allowed for acute TRVs. |
| <b>Option 2</b><br>TCEQ with no total UF maximum                           | 4.2                      | 3                                   | 10                            | 2                     | NA                          | 6                        | 360       | No                                     | No                      | Removes TCEQ's policy of capping the total UFs to 300 for acute TRVs.                                                              |
| <b>Option 3</b><br>Petition                                                | 5.0                      | 10 <sup>o</sup>                     | 10                            | 3                     | NA                          | --                       | 300       | No                                     | No                      | The proposed TRV is the same as the TCEQ acute value, but some of the UFs are different.                                           |
| <b>Option 4</b><br>Petition with UF <sub>D</sub>                           | 0.8                      | 10                                  | 10                            | 3                     | NA                          | 6                        | 1800      | No                                     | No                      | Compared to the petition, includes an additional UF <sub>D</sub> , which matches the TCEQ UF <sub>D</sub> .                        |
| <b>Option 5</b><br>Petition with UF <sub>D</sub> and lower UF <sub>A</sub> | 2.8                      | 3                                   | 10                            | 3                     | NA                          | 6                        | 540       | No                                     | No                      | Compared to petition, includes the additional database UF <sub>D</sub> , but a lower UF <sub>A</sub> .                             |
| <b>Option 6</b><br>Perry et al. 2023                                       | 5.0                      | 3                                   | 10                            | 10                    | NA                          | --                       | 300       | No                                     | No                      | The proposed TRV is the same as the TCEQ acute value, but some of the UFs are different.                                           |

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**Please let DEQ know if you think there is another good option that is not already on this table.**

\*Additional options include rounding the total UF to one significant digit (e.g., the total UF for Option 2 would be 400 instead of 360). DEQ has observed that this is regularly done by U.S. EPA and ATSDR.

## Compilation of ATSAC Feedback Received

Here is a compilation of worksheets received from ATSAC members as of 5-10-2024. A complete summary of the ATSAC Manganese TRV Meeting, including ATSAC member feedback, is captured in the [ATSAC 4-3-2024 Meeting Minutes Document](#).

| TRV Proposal Name                    | TRV (ug/m <sup>3</sup> ) | Uncertainty Factor (UF) Information |                                                    |                       |                             |                                   |           | Human Equivalent Concentration in TRV?                 | Time Adjustment in TRV?                            | ATSAC Notes                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------|--------------------------|-------------------------------------|----------------------------------------------------|-----------------------|-----------------------------|-----------------------------------|-----------|--------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |                          | UF <sub>A</sub> Inter-species       | UF <sub>H</sub> Intra-species                      | UF <sub>L</sub> LOAEL | UF <sub>S</sub> Sub-chronic | UF <sub>D</sub> Database          | Total UF* |                                                        |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>John Vandenberg<br/>4-26-2024</b> | 1.25 µg/m <sup>3</sup>   | 3<br>Monkey study                   | 10<br>Concern about prenatal and youngest children | 3<br>PBPK model       | NA                          | 3<br>Missing neurobehavioral data | 300       | -                                                      | Yes                                                | LOAEL = 1.5 mg/m <sup>3</sup> from Dorman and Erikson studies with time adjustment from 6 hours to 24 hours yields POD = 1.5/4 = 0.375 mg/m <sup>3</sup><br><br>Rationale similar to Option 4 with time adjustment and use factor of 3 for UF <sub>D</sub> due to lack of neuro data. I've revised this from my prior submission to not double-count lack of neuro data by changing UF <sub>A</sub> to 3. |
| <b>Daisy Dong<br/>4-3-2024</b>       | 1.25 µg/m <sup>3</sup>   | 3                                   | 10                                                 | 10                    | NA                          | 1                                 | 300       | UF <sub>A</sub> =3 is equivalent as calculation of HEC | Yes, from 6h to 24h, POD = 0.375 mg/m <sup>3</sup> | Agree with the LOAEL selection of 1.5 mg/m <sup>3</sup> from the two Rhesus monkey studies in combination; Agree with the UF selection based on arguments from the petition presentation. Disagree with no duration adjustment.                                                                                                                                                                           |
| <b>Susan Tilton<br/>4-3-2024</b>     |                          | 3                                   | 10                                                 | 2                     | NA                          | 3                                 | 180       | No                                                     | Yes                                                | See below. Adaptation of Option 6 to include the time adjustment in TRV as part of the POD and not as an uncertainty factor. In addition, include UF <sub>D</sub> to account for potential in utero/fetal neurotoxicity not included in PBPK model.                                                                                                                                                       |
| <b>John Budroe<br/>4-26-2024</b>     | 0.21 µg/m <sup>3</sup>   | 3                                   | 30                                                 | 6                     | NA                          | 3                                 | 1800      | -                                                      | Yes                                                | LOAEL = 1.5 mg/m <sup>3</sup> , time adjustment from 6 hrs to 24 hrs, POD = 1.5/4 = 0.375 mg/m <sup>3</sup> .<br>UF <sub>H</sub> reflects a subfactor of 3 (UF <sub>H-k</sub> ) to adjust for residual pharmacokinetic differences not accounted for by the PBPK model, and a subfactor of 10 (UF <sub>H-p</sub> ) to account for potential prenatal/child                                                |

|                                                       |                           |    |    |    |   |   |     |               |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------|---------------------------|----|----|----|---|---|-----|---------------|------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                       |                           |    |    |    |   |   |     |               |                                                | susceptibility due to pharmacodynamic differences with adults. UF <sub>D</sub> reflects lack of developmental neurobehavioral data.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Jefferson Fowles</b><br><i>See meeting minutes</i> |                           |    |    |    |   |   |     |               |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>John Stanek</b><br><b>4-29-2024</b>                | 1.25<br>ug/m <sup>3</sup> | 3* | 10 | 10 | - | - | 300 | PBPK<br>used* | Yes 6/24 hr<br>(to account for<br>24 hr value) | Value takes into account the 2 most relevant monkey studies as well as the findings from the PBPK model. In disagreement with not having a duration adjustment for determining a 24 hr value from a 6 hr exposure without having supportive data. A full UF for LOAEL is likely warranted as there is not a defined NOAEL under similar exposure conditions (without making a few assumptions). *If A TRV were based solely on lung effects (Dorman study), comparative species metrics from a particle-based dosimetry model (ie MPPD) would need to be presented to determine an HEC and support U <sub>f</sub> a = 3. |

#### **Additional Notes from Susan Tilton 4-3-2024**

UF<sub>A</sub> – Recommend 3-fold to account for differences in toxicodynamics based on the fact that POD is from non-human primate study in rhesus monkeys and no adjustment is needed for dosimetry.

UF<sub>H</sub> – Intraspecies uncertainty of 10-fold accounts for extrapolation to sensitive populations

UF<sub>L</sub> – I recommend an extrapolation of 2-fold since the observed pulmonary pathology was characterized as mild/minor and reversible. Since I'm recommending to incorporate a time adjustment on the POD calculation, it's not necessary to extend the UF here to account for the fact that the LOAEL is not based on 24 hr continuous exposure scenario.

UF<sub>D</sub> – Recommend a value of 3-fold to account for uncertainty related to the possibility of identifying a lower POD if additional studies were available on the potential for neurotoxicity in offspring from in utero exposure. Should be considered that currently available reproductive and developmental effects were not observed in subchronic studies at higher doses for longer periods and that the incorporated PBPK model accounts for differences due to age during infancy and childhood. It is also important to note that:

- We are already using an UF<sub>H</sub> of 10 to account for extrapolation to sensitive populations in humans
- Current studies suggest that under the exposure scenarios considered (24 hr exposure once per month or continuous exposure over 3 wks) that brain tissue levels were not predicted to be above background and that maternal and fetal blood levels were not changed at airborne concentrations less than 10 ug/m<sup>3</sup> (Yoon et al. 2011)
- Therefore, inclusion of an UF<sub>D</sub> would be considered conservative

Time adjustment in TRV-

I will leave it up to others to suggest how this is done, but if the time adjustment is not accounted for as an uncertainty (which several panel members noted that it should not be), then it should be applied to calculate the POD. The toxicokinetic data available suggest that a steady state is achieved with intermittent/shorter exposures of 6 hr/d, 5d/wk and so the time-adjustment would be a conservative approach. In this case, the UF<sub>L</sub> does not need to account for additional uncertainty associated with the exposure period.

Overall comments,

The TRV for OR DEQ should be updated from 0.3 ug/m<sup>3</sup> using the available data for acute respiratory effects. The LOAEL of 1500 ug/m<sup>3</sup> is a reasonable value based on mild respiratory effects in rhesus monkeys for 90 hrs total.

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Oregon Department of Environmental Quality

# Compilation of ATSAC Responses to Manganese Email on 4-12-2024

## Copy of DEQ Email

**From:** GOECKNER Apollonia \* DEQ <Apollonia.GOECKNER@deq.oregon.gov>  
**Sent:** Friday, April 12, 2024 11:10 AM  
**To:** John Budroe; Dong, Qiaoxiang@CDPR; Jeff Fowles; Tilton, Susan C; Stanek, John; John Vandenberg, Ph.D.  
**Cc:** Holly Dixon; Farrer David G; MACMILLAN Susan \* DEQ; GSKA JR \* DEQ  
**Subject:** ATSAC Meeting 3: Follow Up Manganese Questions  
**Attachments:** Compiled Worksheets - ATSAC Mn TRV Proposal.docx; Dorman et al. 2005.pdf; Erikson et al. 2008.pdf

Hi ATSAC Members,

Thank you all again for your participation and thoughtful feedback during the ATSAC meeting last week.

**New Update:** This week we received a [document from ToxStrategies](#) that includes further clarifications and follow-up after the ATSAC meeting. We also received an [email](#) from the author of the Texas Commission on Environmental Quality (TCEQ) Manganese Development Support Document, Joseph Haney, about the exposure duration adjustment. We wanted to immediately share these documents with you.

**Request:** Based on these additional materials, we compiled three additional questions for you all to answer. Please read the ToxStrategies response document and TCEQ email to provide full context for the questions.

**Please reply-all to this email with your answers to these questions before 4/26.**

1. Does Dorman et al. 2005 (see Table 2 specifically) support ToxStrategies' statement on page 3 of their response document?

*"As such, we would not expect lung tissue levels to be higher following a single 24 hour exposure than that for 6 hours per day, for 15 days (or a total of 90 exposure hours), which is the exposure at the POD." – ToxStrategies Response pg. 3*

If you have questions about Dorman et al. 2005 methods, we attached the paper directly to this email. Figure 1 in Dorman et al. is an overview of the experimental design. Exposure and necropsy procedures are detailed on page 3; for example, Dorman et al. states that "necropsies were performed the day following the last inhalation exposure (i.e., 12-18 hr after termination of the final inhalation exposure)."

2. ToxStrategies highlights TCEQ's guidance related to time adjustments:

*"TCEQ guidance recommends that 'if it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute study can be used as the 24-hour POD without adjustment.'" – ToxStrategies Response pg. 3*

Do you agree that the conditions mentioned in this quote from TCEQ guidance are met in the Dorman et al. 2005 and Erikson et al. 2008 study? Do you agree with the TCEQ guidance?

3. Given the additional information from ToxStrategies and TCEQ, what is your current recommendation about an exposure time adjustment and/or uncertainty factors and why? Attached is a compilation of the three worksheets we received after the 4/3 meeting (see page 2). Please edit the worksheet attachment, if applicable, and email it back to us.

Kearns & West and DEQ are still working on meeting minutes for the 4/3 ATSAC meeting. We will send those to you all to review once they are ready.

Thank you,  
ATSAC Governance Team



**Apollonia (Apple) Goeckner | Program Coordinator**  
Oregon Department of Environmental Quality  
700 NE Multnomah St., Suite 600  
Portland, Oregon 97232 - 4100  
P: 503.869.0026  
Pronouns: She/Her/Hers

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Department of Environmental Quality

## ATSAC Responses

| ATSAC Member                     | ATSAC Member Responses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dr. John Budroe<br>4-26-2024     | <p><u>Question 1:</u> The Dorman et al. (2005) and Erickson et al. (2008) Mn exposures of 6 hr/d, 5 d/wk for 15 days would result in a lesser day-1 exposure than that of a human breathing Mn at the same concentration for the acute TRV time period (24 hours). This indicates that a time adjustment from 6 to 24 hours is appropriate (noted in worksheet).</p> <p><u>Question 2:</u> I would be more likely to support the TCEQ guidance if it read "steady state has been achieved, AND toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration...". In this case, there is no toxicodynamic data available that would justify not using an exposure duration adjustment.</p> <p><u>Question 3:</u> As noted in the response to question 1, an exposure time adjustment should be employed (POD x (6 hours/24 hours) - included in attachment). Uncertainty factors are listed in the attachment.</p>                                                                                                                       |
| Dr. Daisy Dong<br>4-26-2024      | <p><u>Question 1:</u> No, an exposure scenario of 6 hours/day, 5 days/week is different from a continuous exposure of 24 hours, which may cause adverse effects that is irreversible.</p> <p><u>Question 2:</u> No, there is no data indicate that the TK and TD are similar between 6 hour and 24 hour exposure. I would agree with the TCEQ guidance if TK reaches steady state AND TD indicates no additional toxic effects. Duration adjustment should be applied for the 24-hour TRV calculation unless there are experimental data proved to be unnecessary.</p> <p><u>Question 3:</u> My recommendations remain same: need to adjust for duration from 6 hours in Monkeys to 24 hours in humans, UF-A of 3, UF-H of 10, UF for LOAEL-to-NOAEL of 10. It is worth to mention that a LOAEL to NOAEL of 10 is not overly conservative given that the critical effects include neurotoxicity and many brain neurotoxicity biomarkers did change at the LOAEL in monkeys. Also I have less concern of in utero exposure as Mn accumulation in the brain is mainly through inhalation route.</p> |
| Dr. Jefferson Fowles             | <i>DEQ did not receive an additional follow-up response.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Dr. John Stanek<br>4-26-2024     | <i>Emailed DEQ TRV worksheet.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Dr. Susan Tilton<br>4-26-2024    | I don't have any additional recommendations from my prior comments except to comment that an adjustment for time should either be accounted for as uncertainty as part of the UF-L or should be applied to calculate the POD, but it does not need to be accounted for in multiple places. Because of that, I believe the recommendation for a reduced TRV is appropriate and one approaching 0.3 ug/m <sup>3</sup> is reasonable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Dr. John Vandenberg<br>4-26-2024 | <p>Thanks for sending the materials - I reviewed the ToxStrategies response and attachment, the email from Joseph Haney, and the Dorman and Erickson papers.</p> <p>My response to the questions: The Dorman and Erickson exposure conditions of 6 hr/d for 5/wk for 15 days does not address the amount of exposure and accumulation of Mn in the body that would occur for a human breathing 24 hours a day i.e., the duration of the acute TRV. The total exposure after 24 hr would be greater than for 6 hr if the Dorman/Erickson study had used continuous (24 hr) exposures (I do</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

appreciate a 24 hr inhalation exposure would be extremely difficult to implement in a laboratory study). I am not convinced that the data obtained at 15 days relates to this time adjustment. In the summary table I retained a time adjustment from 6 to 24 hours to align the study exposures with the duration of the acute TRV.

I've updated the summary table and revised my UF<sub>a</sub> from 10 to 3 in order to not double-count the lack of neurobehavioral data. I retained a UF<sub>d</sub> of 3 due to lack of neurobehavioral data and evidence from the Erickson paper showing brain effects at 15 days. As Dorman states in the first sentence of the abstract "Neurotoxicity and pulmonary dysfunction are well-recognized problems associated with prolonged human exposure to high concentrations of airborne Mn. "

With the time adjustment and application of a combined UF of 300 the TRV result that I derive is 1.25 ug/m<sup>3</sup>.

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## Holly Dixon

---

**From:** Stanek, John <Stanek.John@epa.gov>  
**Sent:** Wednesday, May 22, 2024 11:19 AM  
**To:** Dong, Qiaoxiang@CDPR; GOECKNER Apollonia \* DEQ; 'John Budroe'; 'Jeff Fowles'; susan.tilton@oregonstate.edu; 'John Vandenberg, Ph.D.'  
**Cc:** Holly Dixon; Farrer David G; GSKA JR \* DEQ; MACMILLAN Susan \* DEQ  
**Subject:** RE: ATSAC Meeting 3: Manganese- Meeting Minutes

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I agree and have a few additional thoughts.

In my opinion, the additional information does still not provide enough justification for not applying a duration adjustment to account for extrapolation from a discontinuous exposure regimen to a continuous 24-hr reference value. (That is, whether tissue dose/effects resulting from a 6-hr exposure to 1.5 mg/m<sup>3</sup> would also result from a 24-hr exposure to 0.375 mg/m<sup>3</sup> or some other concentration.)

I would think the Perry model could have addressed this issue by determining an HEC for 24-hrs by incorporating information from the other models cited where tissue NOAELS were estimated. (Maybe it does but it is not clearly presented?).

In addition, I found it interesting as cited in Table 1 of Perry that TCEQ applied a modified (ten Berge) Cxt to calculate a 1-hr value (using the same Dorman study LOAEL of 1.5 mg/m<sup>3</sup> for respiratory effects). However, they determined not to apply it to extrapolate to 24-hrs – this appears methodologically inconsistent to me and is the one of the bases for this issue. With the appropriate justification, applying the same modified Cxt to extrapolate to 24 hrs would result in an adjusted POD of 0.94 mg/m<sup>3</sup> and a reference value of 3.14 ug/m<sup>3</sup> (using UF of 300). Anyway just an observation.

Thank you,

John

---

**From:** Dong, Qiaoxiang@CDPR <Qiaoxiang.Dong@cdpr.ca.gov>  
**Sent:** Wednesday, May 15, 2024 2:08 PM  
**To:** GOECKNER Apollonia \* DEQ <Apollonia.GOECKNER@deq.oregon.gov>; 'John Budroe' <jdbudroe@gmail.com>; 'Jeff Fowles' <jfowles101@gmail.com>; Stanek, John <Stanek.John@epa.gov>; susan.tilton@oregonstate.edu; 'John Vandenberg, Ph.D.' <john.vandenberg@duke.edu>  
**Cc:** Holly Dixon <Holly.M.Dixon@oha.oregon.gov>; Farrer David G <DAVID.G.FARRER@oha.oregon.gov>; jr.giska@deq.oregon.gov; MACMILLAN Susan \* DEQ <Susan.macmillan@deq.state.or.us>  
**Subject:** RE: ATSAC Meeting 3: Manganese- Meeting Minutes



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The additional information only addressed the pharmacokinetic (PK) difference but not the pharmacodynamic (PD) difference between the continuous 24h exposure and the 6hr/d, 5d/wk for 3 weeks exposure. As I commented earlier, only when both PK **AND** PD indicate no differences between these two exposure scenarios, then it is ok not to do time adjustment. Therefore, my opinion stays same as before.

Thank you,  
Daisy

Qiaoxiang (Daisy) Dong, PhD  
Staff Toxicologist-Risk Assessment Section  
Human Health Assessment Branch  
Department of Pesticide Regulation  
California Environmental Protection Agency  
1001 I Street, Sacramento, CA 95812-4015  
Tel: 916-445-3631

---

**From:** GOECKNER Apollonia \* DEQ <[Apollonia.GOECKNER@deq.oregon.gov](mailto:Apollonia.GOECKNER@deq.oregon.gov)>  
**Sent:** Wednesday, May 15, 2024 8:54 AM  
**To:** 'John Budroe' <[jdbudroe@gmail.com](mailto:jdbudroe@gmail.com)>; Dong, Qiaoxiang@CDPR <[Qiaoxiang.Dong@cdpr.ca.gov](mailto:Qiaoxiang.Dong@cdpr.ca.gov)>; 'Jeff Fowles' <[jfowles101@gmail.com](mailto:jfowles101@gmail.com)>; 'Stanek, John' <[Stanek.John@epa.gov](mailto:Stanek.John@epa.gov)>; 'Tilton, Susan C' <[susan.tilton@oregonstate.edu](mailto:susan.tilton@oregonstate.edu)>; 'John Vandenberg, Ph.D.' <[john.vandenberg@duke.edu](mailto:john.vandenberg@duke.edu)>  
**Cc:** Holly Dixon <[Holly.M.Dixon@oha.oregon.gov](mailto:Holly.M.Dixon@oha.oregon.gov)>; Farrer David G <[DAVID.G.FARRER@oha.oregon.gov](mailto:DAVID.G.FARRER@oha.oregon.gov)>; GISKA JR \* DEQ <[JR.GISKA@deq.oregon.gov](mailto:JR.GISKA@deq.oregon.gov)>; MACMILLAN Susan \* DEQ <[Susan.MACMILLAN@deq.oregon.gov](mailto:Susan.MACMILLAN@deq.oregon.gov)>  
**Subject:** RE: ATSAC Meeting 3: Manganese- Meeting Minutes

EXTERNAL:

Hi ATSAC Members,

Thank you for the feedback on the meeting minutes. We integrated all the feedback we received, and the final meeting minutes are now posted [online here](#).

We also compiled all the ATSAC manganese TRV worksheets ([online here](#)) and ATSAC responses to the follow-up manganese questions ([online here](#)).

**New Update:** We received an additional email from the petitioner on May 7<sup>th</sup>, which included a report from ToxStrategies regarding the time adjustment to the proposed manganese TRV. These additional items from the petitioner are [available online](#).

**Request:** Does any of the additional information from the petitioner influence your opinion on the TRV for acute exposure (24-hour) to manganese? Let us know if you have any follow-up questions for ToxStrategies. We would appreciate to hear your input by **COB Wednesday, May 22<sup>nd</sup>**.

Thanks again,  
ATSAC Governance Team



**Apollonia (Apple) Goeckner | Program Coordinator**

Oregon Department of Environmental Quality  
700 NE Multnomah St., Suite 600  
Portland, Oregon 97232 - 4100  
P: 503.869.0026  
Pronouns: She/Her/Hers

---

**From:** GOECKNER Apollonia \* DEQ

**Sent:** Friday, May 3, 2024 4:58 PM

**To:** John Budroe <[jbudroe@gmail.com](mailto:jbudroe@gmail.com)>; Dong, Qiaoxiang@CDPR <[Qiaoxiang.Dong@cdpr.ca.gov](mailto:Qiaoxiang.Dong@cdpr.ca.gov)>; Jeff Fowles <[jfowles101@gmail.com](mailto:jfowles101@gmail.com)>; Stanek, John <[Stanek.John@epa.gov](mailto:Stanek.John@epa.gov)>; Tilton, Susan C <[susan.tilton@oregonstate.edu](mailto:susan.tilton@oregonstate.edu)>; John Vandenberg, Ph.D. <[john.vandenberg@duke.edu](mailto:john.vandenberg@duke.edu)>

**Cc:** Holly Dixon <[Holly.M.Dixon@oha.oregon.gov](mailto:Holly.M.Dixon@oha.oregon.gov)>; Farrer David G <[DAVID.G.FARRER@oha.oregon.gov](mailto:DAVID.G.FARRER@oha.oregon.gov)>; GISKA JR \* DEQ <[JR.GISKA@deq.oregon.gov](mailto:JR.GISKA@deq.oregon.gov)>; MACMILLAN Susan \* DEQ <[Susan.MACMILLAN@deq.oregon.gov](mailto:Susan.MACMILLAN@deq.oregon.gov)>

**Subject:** ATSAC Meeting 3: Manganese- Meeting Minutes

Hello ATSAC Members,

Thank you all so much for your feedback on the additional information we received after the Manganese meeting.

Please see the attached word document with the meeting minutes. Please be sure to look at the portions of the minutes where your own comments are summarized and check them for accuracy. We also have 2 comments included with some clarifying questions for John Budroe and John Stanek.

Please confirm that this looks accurate, or let us know if we need to make any changes by next **Friday, May 10**.

If you have any questions, let us know.

Best,  
ATSAC Governance Team



**Apollonia (Apple) Goeckner | Program Coordinator**

Oregon Department of Environmental Quality  
700 NE Multnomah St., Suite 600  
Portland, Oregon 97232 - 4100  
P: 503.869.0026  
Pronouns: She/Her/Hers

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**Appendix H: ATSAC Written  
Responses to Discussion Questions  
from ATSAC Meetings #5-7 on the  
Review of TRV Proposals**



# ATSAC Meeting 5-7 Written Responses to Discussion Questions

The purpose of this document is to compile ATSAC member feedback during the DEQ [Toxic Air Contaminant Review and Update Rulemaking](#).

## Background

DEQ and OHA requested written responses from ATSAC members to all questions in [Document #3: ATSAC Meetings #5-7 Discussion Questions](#). These written responses were submitted to OHA in March 2025 and compiled into this document.

## Overall Process

Related Resources

[Document 1: Overview of TRV Review](#)

[Document 2: QC of Toxicity Reference Values](#)

[ATSAC Meeting #4 PPT Slides](#)

## Discussion Questions and Responses

| 1. Do you feel prepared to go through these discussion questions? |                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                      | Response:                                                                                                                                                                                                                                                                                                                                                                                                          |
| John Budroe                                                       | Yes – the material in the several documents and workbooks involve reasonably standard toxicology risk assessment methodology.                                                                                                                                                                                                                                                                                      |
| Daisy Dong                                                        | Yes                                                                                                                                                                                                                                                                                                                                                                                                                |
| John Stanek                                                       | Yes, the prior overview meeting and delivery of materials helped greatly in this regard.                                                                                                                                                                                                                                                                                                                           |
| Susan Tilton                                                      | Yes, appreciate the pre-meeting review of the materials, particularly organization of the workbooks.                                                                                                                                                                                                                                                                                                               |
| John Vandenberg                                                   | Yes, I feel well prepared. There is a lot of information provided to review, so it is appropriate to split the discussion across several ATSAC sessions. It would be useful to provide context as to what may be asked of the ATSAC in the future e.g., I understand a review of diesel exhaust will occur, probably in May, but at the end of that activity will ATSAC be asked to participate in future reviews? |

| 2. What was your experience like preparing for this review process as an ATSAC member? |                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                                           | Response:                                                                                                                                                                                                                                                                                                                                                                                |
| John Budroe                                                                            | There were 197 new TRVs and 107 changed TRVs = 304 TRVs proposed for review. That was a pretty substantial number of chemicals to review in the time from the review materials were made available to the meeting dates. It would have been useful if the review materials (especially Workbooks 1 and 2) had been provided farther in advance of the meeting (an additional 2-4 weeks). |
| Daisy Dong                                                                             | I can follow it through ok, but I have some comments on worksheet 2 and document 3 to improve the transparency.                                                                                                                                                                                                                                                                          |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Stanek     | Somewhat related to question #1 (considering the amount of material to review and tremendous amount of work accomplished), the decision to present and provide several smaller documents focused on specific topics for discussion really helped to streamline and organize the review.                                                                                                                                                                           |
| Susan Tilton    | Focused on learning about processes used, appreciate the organization of materials provided, including the use of links to referenced materials which made accessing them very straightforward.                                                                                                                                                                                                                                                                   |
| John Vandenberg | I was impressed by the clarity of communications by the DEQ/OHA team and the well-organized and extensive materials provided to the ATSAC. As noted above, there was a lot of information to review and it was especially helpful to receive this Discussion Questions document which presents questions for the ATSAC to respond to. This provided focus, but was also open-ended enough for the ATSAC to bring in items for discussion throughout the meetings. |

### 3. Do you agree with DEQ's and OHA's overall process for reviewing and updating TRVs?

| ATSAC Member    | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | The overall TRV update process is generally appropriate to the purpose.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Daisy Dong      | Yes, but with some minor comments (HEC, RfC methods for DEQ derived TRVs)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| John Stanek     | Yes, I agree with DEQ's and OHA's overall process for reviewing and updating TRVs. Given the overall scope of this project, the process and review materials were scientifically sound, well-articulated and clearly presented. The resulting database of reference values provides an efficient resource for use in human health risk assessment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Susan Tilton    | <ul style="list-style-type: none"> <li>Yes, with consideration of questions, clarifications and points below. Generally approve of the tiered approach for proposed TRVs based on available sources. Incorporates prior ATSAC feedback – including providing all available TRV values, including TRVs derived from other states (and not just authoritative sources), rationale for choosing proposed values and prioritizing basing acute TRVs on studies with short-term/acute exposure periods rather than deriving from chronic or intermediate studies.</li> <li>Need to make the cut-off for new data inclusion (or date for included data) clear, as well as the process for updating values (e.g. draft values) as new data is available</li> </ul> Noticed that when workbooks list DEQ as the source, not all of the information in document 4 on the source material reviewed by ATSAC is included. Important to document sources used in publicly available material or make sure the document 4 is referenced. |
| John Vandenberg | Yes, the process for reviewing and updating the TRVs was clear and appropriate. Rounding protocol and the number of significant digits used at various steps in the analysis needs to be clearly described.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

### 4. Do you have any questions related to the Overview of TRV Review document (Document 1)?

| ATSAC Member | Response:                                                                                                                                                                                                                                                                                                                                                  |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe  | No questions – the document was well written and self-explanatory.                                                                                                                                                                                                                                                                                         |
| Daisy Dong   | None.                                                                                                                                                                                                                                                                                                                                                      |
| John Stanek  | For document 1, indicating the number of chemicals without a TRV from the identified list would add to the clarity and completeness of Table 1. This could help characterize any data gaps and how they might be addressed in the future via read-across, QSAR, or other methods especially if you have chemicals of great concern (i.e. exposure) that do |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                 | not have a TRV. Conversely, if the missing values are for chemicals of less concern, that would be worth characterizing as well.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Susan Tilton    | <ul style="list-style-type: none"> <li>When DEQ selected TRVs from among candidate options based on robustness of the critical study – what was considered? Would this include making sure adverse health outcomes (or which outcomes) are being evaluated?</li> <li>Cancer and non-cancer TRVs used the most recent source – this was discussed at a prior meeting, but were details about the source considered as part of the process? Or were these used as a starting TRV with subsequent modifications applied as described in document 4 (e.g. time adjustments or uncertainty factors)? I know parameters were documented in the TOA worksheet for uncertainty factors, POD, endpoint, etc – but was consideration given to the approach used by Oregon DEQ to choose TRVs and rational for prioritizing some parameters over others (not necessarily using the most recent source)?</li> </ul> |
| John Vandenberg | This document is undated. It is very important to be clear as to the dates through which the analyses were updated. The first paragraph of the Overview document refers to the cancer risk level ( $10^{-6}$ ) as target for TRV, but does not there provide a definition for non-cancer endpoints. Document 4 provides a list of abbreviations, but not the full definition for the various terms e.g., RfC, TRV, etc. The approach assumes the meanings of the terms are consistent across authoritative sources – yet this may not be the case.                                                                                                                                                                                                                                                                                                                                                      |

| 5. Do you agree that the quality control process was adequate? (Document 2) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                                | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| John Budroe                                                                 | The update quality control process was adequate.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Daisy Dong                                                                  | Seems to be adequate, one question is the transcription from worksheet 2 to worksheet 1 and its QC process.                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Stanek                                                                 | Yes, the QC process was adequate and that any errors identified during compilation and review were transparently described. In addition, the selection of the “Authoritative Sources” used as the primary basis for TRV collation was appropriate.                                                                                                                                                                                                                                                                        |
| Susan Tilton                                                                | Yes, requested more information on the QC process for confirmation of hazard index designation (e.g. HI3 vs. HI5) and to indicate whether these designations contribute to the final TRV since a significant part of the QC focused on this.                                                                                                                                                                                                                                                                              |
| John Vandenberg                                                             | I agree that the quality control process was adequate but I recommend this contractor document be an attachment to a document authored by the DEQ/OHA, making it an Oregon document, not just a contractor report. In that Oregon document indicate what the DEQ/OHA staff did to identify tasks for the contractor and activities by the contractor and DEQ/OHA staff in checking the results. Furthermore, please look closely to use of terminology and include definitions of terms such as “substantial difference”. |

## ATSAC Workbooks

Related Resources

[Workbook 1: DEQ Proposed TRVs](#)

[Workbook 2: TRV Derivation](#)

## Discussion Questions and Responses

## 1. Did Workbooks 1 and 2 capture the right information?

| ATSAC Member    | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | The information in Workbooks 1 and 2 was ample and well-chosen.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Daisy Dong      | <p>--Yes, they captured most necessary information, but I would prefer to include the POD, IUR (slope factor)-see my suggestion in the Workbook 2</p> <p>--Simplify some other information (e.g., for acute, the duration adjustment is 24hr, so no need a column for that; same for chronic, the duration adjustment is 24h/day, 7 days per week;</p> <p>--POD method, POD values, POD Duration adjustment before UF columns</p> <p>--HEC-just provide the value instead of yes or no (also when use DAF =1, it is also a form of HEC calculation as it will affect UF<sub>a</sub> TK portion)</p> <p>--Specify "animal"</p> <p>--"Duration of exposure" can be incorporated into the critical effect, e.g. in a 13 wk rat study</p> <p>--Cancer: Source TRV, better to say "Source IUR" as some agencies use <math>1 \times 10^5</math> instead of 1 in a million</p> <p>--By re-arranging the columns and providing more details in workbook 2, permitting greater transparency as future employees or ATSAC members can calculate the value for accuracy within this workbook directly.</p> <p>--Future ATSAC members may only need to focus on review worksheet 2 and one single companying document (combine all other documents into one single SOP-like PDF and assign section numbers and bullets to different rules, and reference these rules in the Workbook with a hyperlink) (Consider doing this for your future updates).</p> |
| John Stanek     | Yes, these workbooks/databases provide comprehensive information as a resource for TRVs. Each TRV entry provides information on study, duration, endpoint as well the numerical inputs to reproduce the TRV derivations. Both workbooks/databases are well-organized and clearly and thoroughly convey the intended information and complement one another.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Susan Tilton    | I primarily used these as a reference for evaluating the processes used by DEQ for deriving TRVs and appreciated reviewing these during the initial meeting to orient us to their layout. Not all information/values used for deriving TRVs is shared in the workbooks – for example, POD, IUR, cancer slope factor. Because of the detail provided for the other values, e.g. UFs, used, this stands out as missing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| John Vandenberg | The Workbooks provide a very impressive compilation of relevant information to derive and document the TRV work. It is clear this was a very large effort and the resulting workbooks are potentially useful for decisions by the State of Oregon, and by other groups. I suggest addition of three columns to the Workbooks: 1) Indicate the date the data were included to each data row; 2) Add the Inhalation Unit Risk (IUR) for the cancer results, when available; and 3) document whether Age Dependent Adjustment Factors (ADAF) per U.S. EPA (2005) supplemental guideline for early life exposure, were applied. Furthermore, indicate that the IUR from USEPA assessments published prior to 2005 did not apply ADAFs and the quantitative effect when ADAFs are applied is about a 60% increase in lifetime cancer risk (see #2 below).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

## 2. Did you identify any systemic or thematic problems with either workbook that could be improved?

| <b>ATSAC Member</b> | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe         | No problems were noted with either Workbook 1 or 2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Daisy Dong          | See above                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| John Stanek         | <p>In agreement with others who provided more detail, a subset of columns should be reordered that would align more closely with the process of TRV derivation. For example, starting a reordering from the endpoint (column Q?) → POD → Duration info → Duration adjustments → DAF → HEC → UFs → Notes etc., Reordering would help increase clarity/reproducibility for TRV derivation.</p> <p>In addition, the characterization of the HEC/DAF language in the workbook and QC document is confusing/misleading relative to derivation procedures. From a methodological standpoint, if the DAF = 1 that does not mean that the HEC is "no". A DAF = 1 is still an adjustment and reduces the TK/TD UF to 3. Typically it is used for systemic effects and is based on differences in animal and human blood:air partition coefficients. However, it sometimes might be used for other effects depending on the histopathology and location of effect, chemical reactivity and solubility etc., A narrative/rationale for DAF selection is usually provided. Thus, the HEC is the result of the duration adjusted POD and the DAF irrespective of the "numerical value" of the DAF.</p> |
| Susan Tilton        | None observed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| John Vandenberg     | <p>Per response just above (Question #1) the application of Age Dependent Adjustment Factors (ADAF) to the unit risk estimates is not clear. Refer to the 2005 Supplemental Guidance for Assessing Susceptibility from Early-Life Exposures to Carcinogens.</p> <p><a href="https://www.epa.gov/risk/supplemental-guidance-assessing-susceptibility-early-life-exposure-carcinogens">https://www.epa.gov/risk/supplemental-guidance-assessing-susceptibility-early-life-exposure-carcinogens</a></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| <b>3. Are there any missing functionalities in Workbooks 1 or 2 or functions that should work differently that we could improve for the next time we do TRV updates?</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ATSAC Member</b>                                                                                                                                                      | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Budroe                                                                                                                                                              | No suggestions for Workbook 1 and 2 function additions or changes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Daisy Dong                                                                                                                                                               | I personally prefer to include information from workbook 1 into workbook 2, thus reviewers only need to review ONE single workbook (highlight cases that proposed values higher than the initial values-call for reviewers' attention. In a separate workbook, it is time consuming to go between different worksheet to review the information). Also highlight cases that have ambiguity in conforming the rules specified by DEQ (for most cases, if reviewers agree with the rules then there is no need to review all individual cases). Could do something like this: state the reason for why choose one authority over the other and cite the selection criterion A, B, C, D etc.). This way, reviewers can spend their time on the most needed cases. |
| John Stanek                                                                                                                                                              | No additional functionalities from those that were discussed as a group during the committee meetings.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Susan Tilton                                                                                                                                                             | It was suggested to set up rules applied to TRV selection and then reference which rules were applied in the case of calculated TRVs. I would agree with this approach in the future as it would help to standardize the review process. As mentioned above, a date stamp for data and adding details for sources described in document 4.                                                                                                                                                                                                                                                                                                                                                                                                                     |



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| John Vandenberg | Having the workbooks online with links between the workbooks would be very useful e.g., to add search features to enable all information for specific chemicals to be readily identified and pulled into summary form. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4. Were you able to access all the information you needed to make decisions about whether to support DEQ's proposed TRVs?

| ATSAC Member    | Response:                                                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | The information supplied was sufficient for the purpose.                                                                                                                                  |
| Daisy Dong      | Yes                                                                                                                                                                                       |
| John Stanek     | Yes, all the information was provided to support my decision making. In random testing of links to the resource and reference information provided, everything was accessible.            |
| Susan Tilton    | I primarily used these as a reference for evaluating the processes used by DEQ for deriving TRVs and appreciated reviewing these during the initial meeting to orient us to their layout. |
| John Vandenberg | I found the information was available except that information on application of ADAFs for carcinogens was not indicated.                                                                  |

## 4: Proposed TRVs Where DEQ is the Authoritative Source

Related Resources

[Document 4: Proposed TRVs Where DEQ is the Authoritative Source](#)

### Discussion Questions and Responses

#### 1. What feedback or concerns do you have about the way DEQ proposes to adjust acute TRVs for exposure time in many cases (Section 2)?

| ATSAC Member | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe  | The methods listed in Section 2 for extrapolating from 1-hour acute TRVs to 24-hour acute TRVs and for extrapolating from subchronic TRVs to 24-hour acute TRVs are generally acceptable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Daisy Dong   | See my comments on Document 4 for questions 1 to 7.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| John Stanek  | No concerns noted with the proposal to adjust acute TRV for exposure times. The proposal is supported to my knowledge by current science and practices. In the cases where a subchronic study is used to calculate the acute TRV, consideration should be given to providing discussion or characterization of the potential uncertainty and/or conservative health protectiveness of these values. In the majority of these cases, a relatively minor adjustment is used to extrapolate from studies greater than 30 days in duration which result in 24-hr TRVs similar to subchronic TRVs.                                                                                                         |
| Susan Tilton | Described the default values used for exponent n when reflecting the influence of concentration relative to exposure time. Should be noted when Haber's Law was applied with or without the ten Berge adjustment – only seems that it was noted if an empirical value was used if it was different than n=1. In section 2.3, since Haber's Law with ten Berge adjustment was not used for extrapolating from longer exposure duration to a shorter one with the exponent n=3 as outlined in the prior section, should be clear about time adjustments from subchronic exposures to acute where the only adjustment was to remove 'days per week' to account for the intermittent exposures over time. |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| John Vandenberg | The documentation on proposed TRVs where DEQ is the authoritative source was thorough and necessary to understand the approach applied and analyses for individual chemicals. I recommend the document reference the OECD acute assessment document provided by John Stanek. Daisy Dong made some useful recommendations for <i>future, not current</i> , adjustments to Points of Departure (POD) using molecular weight, and exposure time used in principal study, not just from 1 hour to 24 hour (which Equation 4 seems to show). Adding example calculations using data from a chemical in the table will be helpful for users of these documents when equations are shown. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>2. Are there any specific TACs in section 2 to which Haber's Law should not be applied to adjust exposure time?</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ATSAC Member</b>                                                                                                    | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| John Budroe                                                                                                            | No chemicals in section 2 where the application of Haber's Law would be inappropriate (e.g. sensory irritation-inducers or developmental toxicants) were noted.                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Daisy Dong                                                                                                             | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| John Stanek                                                                                                            | None identified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Susan Tilton                                                                                                           | For chemicals in which the endpoint is listed as respiratory and eye irritation, is it confirmed which endpoint the POD is derived? In some cases (e.g. benzyl chloride, phenol, selenide), both endpoints are listed and Haber's Law is presumably being applied even though this should be an exception (for eye and mucous membrane irritation) because the effect would be concentration-dependent and not time dependent. I don't see this described in Workbook #2 (actually found this in a different column for target organ so don't know if this could be clearer in the workbook) |
| John Vandenberg                                                                                                        | None that I know of.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| <b>3. What feedback or concerns do you have about the cases where DEQ proposes to apply toxicity information from a better studied TAC to a lesser studied, structurally similar TAC (Section 3)?</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ATSAC Member</b>                                                                                                                                                                                   | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| John Budroe                                                                                                                                                                                           | No concerns for the chemicals listed in Section 3.                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Daisy Dong                                                                                                                                                                                            | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| John Stanek                                                                                                                                                                                           | No concerns noted. Using information from structurally similar chemicals for chemicals that are data poor reflects the current state-of-the-science for use in hazard assessment.                                                                                                                                                                                                                                                                                                                                                |
| Susan Tilton                                                                                                                                                                                          | No concern for the use of TEFs for polybrominated biphenyls, polybrominated dibenzo-p-dioxins and dibenzofurans as that uses a recommended approach discussed the literature with feedback from ATSAC. I also agree with the use of RPFs applied to crotonaldehyde; however, in general would recommend that the rationale for read-across be provided by DEQ even if referencing another agency's method for derivation, particularly when not from an authoritative source. This would also apply to N-propylbenzene and PFOS. |
| John Vandenberg                                                                                                                                                                                       | Please review the acrolein entry in workbook 2; the noncancer chronic TRV is 0.9 ug/m3 derived from ATSDR, but the IRIS RfC is 0.02 ug/m3 (2003), and the workbook doesn't show multiple authoritative sources.                                                                                                                                                                                                                                                                                                                  |

#### 4. What feedback or concerns do you have about cases where DEQ proposes to modify TRVs by changing uncertainty factors (Section 4)?

| ATSAC Member    | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | <p>In Table 3, DEQ (TRVs where DEQ Proposes to Modify Uncertainty Factors Applied by Originating Source Agency) proposes to change the acetone LOAEL to NOAEL uncertainty factor (UF) from 2 (used by TCEQ) to 3, stating that "DEQ proposes to increase TCEQ's LOAEL to NOAEL UF from 2 to the more standard 3 used by all DEQ's authoritative sources (TCEQ 2015), raising the total UF from 20 to 30". OEHHHA uses a LOAEL to NOAEL UF of 10 for all chronic REL derivations. DEQ should clarify this, and consider whether a LOAEL to NOAEL UF of 10 should be used in this situation.</p> <p>Additionally, Table 3 of Section 4 lists a proposed acute TRV of 12,000 µg/m<sup>3</sup> for n-hexane based on an uncertainty factor modification to the 2017 TCEQ acute ReV. Table 1 of Document 7 (Proposed TRVs Not Yet Finalized by Authoritative Sources) lists a proposed acute TRV of 21,000 µg/m<sup>3</sup> for n-hexane based on a draft ATSDR acute MRL. DEQ should clarify which n-hexane acute TRV it intends to adopt.</p> |
| Daisy Dong      | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Stanek     | In certain instances, revise the language about the UF application of 2 to 3 for use of a LOAEL in place of a NOAEL. The EPA default is 10 not 3 so this does not apply to all authoritative sources as currently written. A UF is not applied if BMD modeling is used to determine the POD. This was discussed in the committee meetings.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Susan Tilton    | Agree with proposed changes in UFs to bring approach in line with DEQ authoritative sources and standard OR DEQ processes (for example, in cases where uncertainty for the extrapolation is needed – subchronic to chronic). As mentioned earlier, when a source is listed as DEQ in the table rather than a non-authoritative sources (TCEQ, for example), it would be helpful to have this process documented for reference in the Worksheets. It is well described in document 4.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| John Vandenberg | The documentation and modifications appear appropriate and the brief narrative is helpful. From the ATSAC discussion my notes indicate the acetone writeup should change UF <sub>D</sub> = 1 and UF <sub>L</sub> = 10.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

#### 5. Do you have feedback or concerns about cases where DEQ proposes to derive TRVs by making other types of modifications to values developed by other agencies (Section 5)?

| ATSAC Member    | Response:                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | The TRVs derived using modifications to chemical health values derived by other agencies (Section 5, Table 4) appear to be appropriate. |
| Daisy Dong      | <i>blank</i>                                                                                                                            |
| John Stanek     | No concerns noted.                                                                                                                      |
| Susan Tilton    | None                                                                                                                                    |
| John Vandenberg | From the ATSAC discussion my notes indicate hydrazine should be included in table 2.                                                    |

#### 6. Do you have any feedback or concerns about DEQ using the list of relative potency factors provided by the [Minnesota Department of Health](#) for carcinogenic PAHs (using the 2017 IRIS IUR for benzo[a]pyrene as the index) (Section 5 table 6)?

| <b>ATSAC Member</b> | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe         | No concerns about using the Minnesota Department of Health carcinogenic PAH relative potency factors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Daisy Dong          | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| John Stanek         | No concerns noted.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Susan Tilton        | The proposed updates utilize the same RPF from 2018, but is now applying it to the IUR for benzo[a]pyrene (2017 EPA IRIS) rather than the older OEHHA IUR. So the process has not changed and the RPFs are the same, derived similarly (presumably, difficult to find original information as some links in the MDH document do not work). It should be noted that ATSDR provides guidance (2022) on PAH relative potency factors, which seems it would be an authoritative source compared to MDH. I have not looked at it in detail, but don't know if DEQ considered this source. |
| John Vandenberg     | I support the use of the Minnesota Department of Health relative potency factors. The use of other sources of values that are not listed in the Oregon Rule as authoritative, such as MN, CT, NY etc was discussed at outset of this review and I understand with ATSAC agreement the use of other sources is acceptable based on careful consideration by DEQ/OHA and ATSAC.                                                                                                                                                                                                        |

**7. Do you have feedback or concerns about any of the TRVs that DEQ is proposing to adopt without modification from non-authoritative (i.e., not EPA, ATSDR, or CalEPA) sources (Section 6, Table 7)?**

| <b>ATSAC Member</b> | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe         | No concerns regarding the TRVs proposed in Section 6, Table 7.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Daisy Dong          | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| John Stanek         | No concerns noted. However, either provide a brief summary about what criteria these sources lack (in general) that makes them non-authoritative or link back to the source where this is outlined.                                                                                                                                                                                                                                                                                                                                                                                                           |
| Susan Tilton        | I don't have any issues with these sources as long as the same criteria are being met in terms of how Oregon DEQ accepts the TRV values. This has primarily been used to adopt chronic and acute TRVs and are described in detail through TCEQ documents or DEQ July 2024 memorandum summarizing available TRVs and parameters used to derive them. Will the information in the memorandum be public as a source – or links to the original sources used in the memorandum? There is not description in the worksheets about the source for these new TRVs other than having DEQ as the authoritative source. |
| John Vandenberg     | I have no concerns about adoption of the other values as identified in Table 7. I recommend addition of b(a)p to this table for completeness.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

**8. Pending DEQ and OHA consideration of ATSAC comments in previous discussion questions, do you agree with the TRVs where DEQ (in consultation with ATSAC) is the proposed authoritative source?**

| <b>ATSAC Member</b> | <b>Response:</b>                                                                                                                                                                          |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe         | The TRVs where DEQ (in consultation with ATSAC) is the proposed authoritative source are generally acceptable. Some suggested reconsiderations are noted in the question responses above. |
| Daisy Dong          | Yes                                                                                                                                                                                       |

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| John Stanek     | Yes, I agree with the proposed TRVs where DEQ is the proposed authoritative source.                                                              |
| Susan Tilton    | I agree with the process as discussed in the meeting with considerations made for referencing the process in the workbooks as described earlier. |
| John Vandenberg | I agree with the TRVs where DEQ (in consultation with ATSAC) is the proposed authoritative source.                                               |

### 9. What feedback do you have related to the *Proposed TRVs Where DEQ is the Authoritative Source* document?

| ATSAC Member    | Response:                                                                                                                                                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | No feedback in addition to the answers to the document questions already answered.                                                                                                                                                                                       |
| Daisy Dong      | Suggest to include a summary table for all default settings (especially UFs) from the authoritative sources (EPA, ATSDR, CalEPA).                                                                                                                                        |
| John Stanek     | No additional feedback.                                                                                                                                                                                                                                                  |
| Susan Tilton    | There is a lot of supporting information used for deriving TRVs and so it should be considered how to best make that information publically available and not lose connection to the workbooks.                                                                          |
| John Vandenberg | My only comment is that the documentation by OHA/DEQ is highly informative, well organized and very useful. I commend the staff for the great work they have done as it demonstrates depth of knowledge and thoughtful consideration for ATSAC to review and comment on. |

## 5: Proposed Groupings of Toxic Air Contaminants

Related Resources

[Document 5: Proposed Groupings of Toxic Air Contaminants](#)

### Discussion Questions and Responses

#### 1. Do you have any feedback or concerns about how we plan to organize groups of chemicals and how we plan to account for their toxicity?

| ATSAC Member    | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | The organization of chemical groups in this document is generally well done. One suggested addition to Section 4.1 (Metals) would be an explicit statement in the section text that those groupings do not apply to organometallic compounds. Additionally, in Section 2, Table 1, the entry for toluene diisocyanate (TDI) isomers (CAS: 26471-62-5) in column 3 (Difference in approach from existing rule) needs to be corrected. The OEHHA REL listing covers mixed TDI isomers, 2,4-TDI and 2,6-TDI as a group, not separately. |
| Daisy Dong      | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| John Stanek     | No concerns noted with the document or organization of the chemicals.                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Susan Tilton    | In the future, would consider documenting or reporting how similarity for groupings is defined by sources when utilized by DEQ.                                                                                                                                                                                                                                                                                                                                                                                                      |
| John Vandenberg | I have no concerns, the organization of chemicals appears appropriate.                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| 2. Do you agree that these are the right compounds within each group? |                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                          | Response:                                                                                                                                                                                                                                                                                                                                        |
| John Budroe                                                           | The selection of the compounds within each group are appropriate.                                                                                                                                                                                                                                                                                |
| Daisy Dong                                                            | Yes. Question related to the size for crystalline silica (4µm vs. 10 µm): I did some search and I think the common acceptable consensus is 4 µm.                                                                                                                                                                                                 |
| John Stanek                                                           | Yes, it appears the right compounds have been assigned within each group. The approach to group various chemicals and metals is consistent with other agencies as cited throughout the document. For example, a similar grouping approach was used by EPA in their assessment of trimethylbenzenes as are the groupings of metals and compounds. |
| Susan Tilton                                                          | No concerns                                                                                                                                                                                                                                                                                                                                      |
| John Vandenberg                                                       | Yes, to the best of my knowledge the right compounds are included within each group.                                                                                                                                                                                                                                                             |

| 3. The World Health Organization (WHO) has a <a href="#">2024 set of toxic equivalency factors (TEFs)</a> for dioxins and furans. DEQ is currently proposing to keep using the 2010 EPA TEFs as applied by OEHHHA. No other jurisdictions have adopted the new WHO TEFs to DEQ's knowledge. Should DEQ continue to apply EPA's 2010 recommended TEFs as proposed or consider proposing the 2024 WHO TEFs instead (Section 3.1)? |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                                                                                                                                                                                                                                                                                                                                                                                    | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| John Budroe                                                                                                                                                                                                                                                                                                                                                                                                                     | DEQ should continue to use the 2010 EPA TEFs for the present. DEQ may wish to consider using the 2024 WHO TEFs if one of their external authoritative sources (ATSDR, EPA, OEHHHA) adopts them.                                                                                                                                                                                                                                                                                                    |
| Daisy Dong                                                                                                                                                                                                                                                                                                                                                                                                                      | Maybe contact EPA and OEHHHA to see their plan of whether or when they will adopt the new TEFs? I prefer to adopt the new WHO TEFs-better database and methodology.                                                                                                                                                                                                                                                                                                                                |
| John Stanek                                                                                                                                                                                                                                                                                                                                                                                                                     | Continuing with the current proposed approach based on the 2010 TEFs is justifiable. However, careful consideration should be given to determining the feasibility of conducting an independent review and analysis of the newly proposed 2024 TEFs as they would presumably reflect updated science. Consequently, if the WHO approach is recommended after review, DEQ should consider leading the change.                                                                                       |
| Susan Tilton                                                                                                                                                                                                                                                                                                                                                                                                                    | Agree since these have recently been developed and would be consistent with your proposed approach to use authoritative sources. In addition, from examples used in the DeVito et al. 2024 paper, it is estimated that original 2005 TEFs would generally be more health protective/conservative in the short-term. Would determine how EPA plans to incorporate these methods. Also, agree with discussion on consistency regarding reporting of significant digits and how these are determined. |
| John Vandenberg                                                                                                                                                                                                                                                                                                                                                                                                                 | The rationale for not using the WHO 2022 TEFs is not compelling. The WHO document is most current and the authors of that document are well-known experts in the field. I suggest contacting Linda Birnbaum (former Director of NIEHS) for her opinions about the WHO 2022. Though she is an expert in the area of TEFs she was not an author of the document and could provide an independent review based on her extensive experience.                                                           |

## 6: Proposed TRVs Using Screening PPRTVs as the Authoritative Source

Related Resources

[Document 6: Proposed TRVs Using PPRTV Screening Values as the Authoritative Source](#)



## Discussion Questions and Responses

| <b>1. What feedback or concerns do you have related to the <i>Proposed TRVs Using PPRTV Values as the Authoritative Source</i> document?</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ATSAC Member</b>                                                                                                                          | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| John Budroe                                                                                                                                  | The formic acid chronic PPRTV derivation uses a database uncertainty factor (UF) of 10 (lack of inhaled formic acid developmental/multigenerational reproductive studies) and a subchronic (13-week study) to chronic UF of 10. A database UF of 3 is more commonly used, and some authoritative sources (e.g. OEHHA) would apply a subchronic to chronic UF of 3 to a 13-week study. If those alternative UFs were used, the composite UF would be 3,000. |
| Daisy Dong                                                                                                                                   | No concerns.                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Stanek                                                                                                                                  | No concerns noted with the document.                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Susan Tilton                                                                                                                                 | There is a large amount of uncertainty for these values compared to those reported from other sources in the Workbook; however, the purpose of screening PPRTVs by EPA is for initial risk characterization of compounds of concern at Superfund sites. If these are used, it should be flagged to be updated when non-provisional values are available.                                                                                                   |
| John Vandenberg                                                                                                                              | The development of PPTRV values includes standard literature search, application of EPA guidelines, and internal and external peer review steps. The scientists involved in the development and review are experienced health risk assessors and I am confident in the PPRTV methods and results, especially for PPRTVs developed in the about the last 20 years i.e., since about 2003, at which time the PPRTV process became more robust.               |

| <b>2. Is the science behind PPRTV screening values sufficiently robust to use for DEQ's air quality programs, including regulatory applications, when no other toxicity information is available?</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ATSAC Member</b>                                                                                                                                                                                   | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| John Budroe                                                                                                                                                                                           | In general, the risk assessment procedures used to generate the PPRTV screening values are sufficiently robust for DEQ's purposes. However, DEQ might want to consider applying a composite uncertainty factor cap of 3000 to the PPRTV derivations and adjusting those values where necessary.                                                                                                                                                                                       |
| Daisy Dong                                                                                                                                                                                            | Better to have values than no value.                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| John Stanek                                                                                                                                                                                           | Yes. Although they are "screening" values, the process for development of these values is the same as for more data-intensive, higher-tier values and undergo external peer review. The development of these values utilizes well-documented methodologies and the assessment documents supporting these values are transparently presented for their intended application. In my opinion, not having a value as a guide is considerably more uncertain in evaluating potential risk. |
| Susan Tilton                                                                                                                                                                                          | Yes, these values are peer-reviewed and developed using a weight-of-evidence approach. Process to update when non-provisional values are available should be considered.                                                                                                                                                                                                                                                                                                              |
| John Vandenberg                                                                                                                                                                                       | I have confidence in the set of PPRTVs included in Document 6 as appropriate to use as the basis for TRV in the absence of authoritative values.                                                                                                                                                                                                                                                                                                                                      |

## 7: Proposed TRVs Not Yet Finalized by Authoritative Sources

Related Resources

[Document 7: Proposed TRVs Not Yet Finalized by Authoritative Sources](#)

## Discussion Questions and Responses

| 1. Do you have any feedback or concerns about DEQ proposing to use the TRVs listed in this document (Table 1) that are not yet finalized by authoritative sources? |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                                                                                                                       | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| John Budroe                                                                                                                                                        | In general, the development of TRVs from draft authoritative source chemical health values is reasonable and appropriate. However, DEQ should be more explicit regarding what will be done (and when) if the public comments on the draft authoritative source documents result in changed authoritative source chemical health values.                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Daisy Dong                                                                                                                                                         | I agree, simply add a column to the Excel Workbook to indicate the dates for update, thus DEQ can update (finalize or revise) these TRVs based on the progress of authoritative sources.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Stanek                                                                                                                                                        | No concerns noted with using the draft TRVs presented in Table 1. All of these draft values are in the later stages of the review process where typically substantial changes to final values do not occur.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Susan Tilton                                                                                                                                                       | Similar to screening PPRTVs, which are also peer-reviewed, these should be flagged as draft values and updated once finalized. Is the purpose of the TRVs to be a 'living document' updated as changes occur? If so, then draft TRVs can be included until finalized even if after the rulemaking period ends; however, should be consistent.                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| John Vandenberg                                                                                                                                                    | My only concern is the is the timeline for review. My understanding is that it is to occur every 3 years, which suggests for some chemicals there will be no TRV until the next review cycle, yet updated reviews of critically important chemicals may be available sooner than 3 years. I recommend that if the OHA/DEQ become aware of an updated assessment from an authoritative source before the 3-year review cycle that they seek ATSAC evaluation prior to the 3-year assessment. Also, I recommend reviewing available public comments on the draft assessments from authoritative sources, if available. If public comments are not readily available on their draft documents, then I recommend reaching out to ATSDR, OEHHA or USEPA and ask to see the public comments. |

| 2. Would you propose an alternative in the case of any or all these TACs? |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                              | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| John Budroe                                                               | DEQ proposes adopting a draft ATSDR acute MRL of 7 µg/m <sup>3</sup> for acrolein based on human nose and throat irritation and decreased respiratory rate (Weber-Tschopp et al. 1977; LOAEL = 0.3 ppm). The prior acute TRV was based on an OEHHA acute REL (2.5 µg/m <sup>3</sup> ), which was derived from the geometric mean of human eye irritation data from Weber-Tschopp (1977)(LOAEL = 0.07 ppm) and Darley et al. 1960 (LOAEL = 0.06 ppm). ATSDR did not cite Darley et al. (1960). Since both authoritative sources used at least one common study to develop acute acrolein health values, the OEHHA REL is based on an endpoint (sensory irritation) not requiring exposure time adjustment and the OEHHA REL is more health-protective, DEQ should consider retaining the OEHHA acute acrolein REL as the basis for the acute acrolein TRV. |
| Daisy Dong                                                                | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| John Stanek                                                               | No proposed alternative.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Susan Tilton                                                              | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| John Vandenberg                                                           | I do not have any alternative to recommend for any or all of these TACs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |



## General Questions

Related Resources

All materials linked in [Document 1: Overview of TRV Review](#)

## Discussion Questions and Responses

| 1. Did you find any errors or have any feedback or concerns about the content in any of the ATSAC review materials? |                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                                                                        | Response:                                                                                                                                                                  |
| John Budroe                                                                                                         | No general feedback or concerns regarding the ATSAC review material content.                                                                                               |
| Daisy Dong                                                                                                          | None                                                                                                                                                                       |
| John Stanek                                                                                                         | No additional concerns noted that have not already been addressed during the committee review meeting or reflected elsewhere in the responses to the discussion questions. |
| Susan Tilton                                                                                                        | <i>blank</i>                                                                                                                                                               |
| John Vandenberg                                                                                                     | <i>blank</i>                                                                                                                                                               |

| 2. Do you have any feedback or concerns about a specific toxic air contaminant TRV that we have not discussed or flagged anywhere else? |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member                                                                                                                            | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Budroe                                                                                                                             | DEQ proposes to use the ATSDR 2017 toluene chronic MRL instead of the OEHHA 2020 toluene chronic REL as the basis of the toluene chronic TRV. DEQ's reason for this decision provided in Workbook 2 is "For chronic TRV, DEQ proposes to use ATSDR over OEHHA and IRIS values. While OEHHA's value was published more recently, it is based on fewer and older studies than the ones ATSDR used." ATSDR does use newer studies as the basis of its MRL (Schaper 2003, 2004, 2008; Seeber 2004, 2005; Zupanic 2002) compared to the study primarily used by OEHHA (Zavalic 1998). However, ATSDR used a NOAEL of 45 ppm as the point of departure (POD) for developing its chronic MRL. In contrast, OEHHA used a benchmark concentration (BMCL <sub>05</sub> ) of 12 ppm to develop its chronic REL. So, while the ATSDR data set used to develop the chronic MRL is newer than the OEHHA data set, the OEHHA derivation uses a newer and more preferred extrapolation method (benchmark concentration) than that used by ATSDR (NOAEL/LOAEL). It should also be noted that combined with different uncertainty factors used by ATSDR and OEHHA, the TRV based on the OEHHA REL is approximately 9-fold less than the TRV based on the ATSDR MRL. DEQ should reexamine their source choice for the toluene chronic TRV. This example also illustrates the necessity for DEQ to consider extrapolation methods when determining which authoritative source TRV has the "newest science". |
| Daisy Dong                                                                                                                              | I made some additional comments on chronic TRVs for 1-bromopropane, methanol, and toluene and acute TRVs for 2-Butanone and Chromium (see details in Workbook 2-Column ATSAC notes).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| John Stanek                                                                                                                             | No concerns noted.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Susan Tilton                                                                                                                            | <i>blank</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                    |              |
|--------------------|--------------|
| John<br>Vandenberg | <i>blank</i> |
|--------------------|--------------|

## Contact

Oregon Department of Environmental Quality  
Cleaner Air Oregon Program  
[cleanerair@deq.oregon.gov](mailto:cleanerair@deq.oregon.gov)

## Prepared By:

This document was prepared by Oregon Health Authority. Authors:

Holly Dixon, PhD  
Public Health Toxicologist

David Farrer, MS, PhD  
Public Health Toxicologist

Dana Crosby, MPH  
Environmental Health Assessment Program Coordinator



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# **Appendix I: ATSAC Written Responses to Discussion Questions from ATSAC Meeting #8 on Diesel Particulate Matter**



# ATSAC Written Responses to Diesel Particulate Matter Discussion Questions

The purpose of this document is to compile ATSAC member feedback on the cancer toxicity reference value (TRV) for diesel particulate matter (DPM) during the DEQ Toxic Air Contaminant Review and Update Rulemaking.

## Background

This DEQ and OHA requested written responses from ATSAC members to all questions in the [Diesel Particulate Matter Framing Document](#). These written responses were submitted to OHA in May 2025 and compiled in this document.

## Related Resources

[Diesel Particulate Matter Framing Document](#)

[ATSAC Meeting #8 PowerPoint Slides](#)

[ATSAC Meeting #8 Agenda](#)

## Discussion Questions and Responses

| 1. Do you see additional uncertainties with the proposed cancer TRV not already covered in the DPM Framing Document? |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ATSAC Member:                                                                                                        | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| John Budroe                                                                                                          | The DPM Framing document did a commendably thorough job of discussing the uncertainties associated with adopting the OEHHA diesel particulate matter (DPM) inhalation unit risk (IUR) for use in developing a cancer TRV. The only area that might benefit from some additional discussion would be early-life sensitivity (infants and children).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Daisy Dong                                                                                                           | I do not see any additional uncertainties.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| John Stanek                                                                                                          | Overall, the framing document is well organized and clearly presented. The document could benefit from additional discussion highlighting the various uncertainties outlined in the CalEPA risk assessment report and the Ramboll white paper.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Susan Tilton                                                                                                         | <ul style="list-style-type: none"><li>• Primary uncertainties are:</li><li>• Lack of dose-dependency in studies used to derive TRV (i.e. risk did not increase with duration of employment or age in railroad worker studies from 1987 &amp; 1988) - likely due to<ul style="list-style-type: none"><li>○ the fact that the study used job title as a surrogate for DPM exposure, which likely led to misclassification</li><li>○ the year when exposures began is unknown as diesel technology was just gradually being introduced through 1950s</li><li>○ lack of information on other occupational exposures</li><li>○ also method of analysis resulted in different outcomes by different groups</li></ul></li><li>• Diesel exhaust from past epidemiological studies would not be consistent with exposure to current technologies</li></ul> |

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|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                 | <ul style="list-style-type: none"> <li>US EPA (2002) concluded that even though the scientific evidence support an association between DPM and lung cancer, the available data were too uncertain to be used as the basis of a quantitative dose-response analysis and subsequent derivation of cancer unit risk for diesel exhaust</li> <li>One way to address uncertainty related to causality in epidemiological studies is using the Hill Criteria – this was addressed by CalEPA and recommend to include in the framing document</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| John Vandenberg | <p>The DPM Framing Document (2025) appropriately identifies and discusses in a balanced manner uncertainties evaluated by several organizations that have conducted extensive work to understand and apply state-of-the-art risk assessment methods to derive a quantitative cancer potency estimate for DPM.</p> <p>A consideration not discussed in the DPM Framing Document is that none of the existing DPM cancer potency assessments appear to consider age as a risk factor. The Supplement to the 2005 USEPA Guidelines for Carcinogen Risk Assessment identifies the potential for additional risk to children due to a variety of biological and exposure differences with adults, hence Age Dependent Adjustment Factors (ADAF) are applied to carcinogens that have a mutagenic mode of action, which is relevant for DPM (see IARC). I am not proposing that ADAFs be applied to the OEHHHA (1998) or other assessments, but that this consideration be more explicitly discussed in the DPM Framing Document.</p> |

**2. It appears Ramboll Environ (see Table 1 of Ramboll Environ’s white paper) calculated an inhalation unit risk (IUR) for Vermeulen et al. 2014 using an excess lifetime cancer risk of 17 per 10,000 at a DPM-proxy (elemental carbon) concentration of 1 µg/m3 (see Table 2 of Vermeulen et al. 2014). What do you think about Ramboll’s approach and DEQ’s interpretation of where that IUR came from?**

| <b>ATSAC Member:</b> | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe          | DEQ’s interpretation of how Ramboll Environ developed a DPM-proxy (elemental carbon; EC) IUR from the Vermeulen et al. (2014) data appears to be accurate. The approach taken by Ramboll could eventually be the starting point for developing a DPM IUR, but a number of details (e.g. conversion of an EC IUR to a DPM IUR) would have to be worked out in order to produce a useable DPM IUR from the Vermeulen et al. (2014) data. The DPM Framing Document states: “DEQ and OHA do not support deriving a new DEQ cancer TRV at this time because this would take a considerable amount of toxicology resources (staff, time, and money), and even with recent higher quality studies available, considerable uncertainties remain and a derivation effort at this time may not result in an alternate, more robust cancer TRV. ” DEQ and OHA are entirely correct. |
| Daisy Dong           | DEQ’s interpretation of Vermeulen 2014 is correct.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| John Stanek          | It appears that DEQ’s interpretation of Ramboll’s approach and calculation of an IUR from Vermeulen is correct based upon the information provided.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Susan Tilton         | <ul style="list-style-type: none"> <li>In the Ramboll white paper, a range of risk values were identified due to the high uncertainty associated with the different methods to develop quantitative estimates from the more recently published diesel miners and truckers studies. The Vermeulen paper itself was a meta-analysis of 3 studies – which was subsequently modified based on comments and reanalyzed by others (Crump and Morfield and Spallek) using different methods. The primary conclusion is that a consensus does not exist for the analysis of these datasets.</li> <li>However, the strength of the Ramboll white paper is that it relies on newer studies that HEI recommends for use in quantitative risk assessment and, therefore, are a good comparator to values calculated by CalEPA.</li> </ul>                                            |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Vandenberg | <p>Table 2 of Vermeulen et al (2014) shows estimates of lifetime risk per 10,000 for the general public ages 5-80 years, and for workers exposed at ages from 20 to 65 years. The estimate for the general public is most appropriate to evaluate and for an average exposure of 0.8 ug/m<sup>3</sup> the risk from age 5 through age 80 is 21 per 10,000. To calculate the risk URE for an exposure of 1 ug/m<sup>3</sup>, the risk is 21/(1/0.8) = 16.8 which rounds to 17 per 10,000, as shown in Table 1 of the Ramboll Environ white paper as 1.7 x 10<sup>-3</sup> per ug/m<sup>3</sup>. The DEQ characterization of the derivation shown in the Ramboll Environ white paper appears to be correct. However, the derivation by Ramboll Environ does not include consideration of Age Dependent Adjustment Factors applied to ages 0-2 and 2-6 from the Supplement to the 2005 EPA Guidelines for Carcinogen Risk Assessment. This is an important omission in the Ramboll Environ white paper.</p> <p>Web address for Ramboll Environ white paper: <a href="https://www.portseattle.org/sites/default/files/2018-03/T5_FEIS_volume_II_Appx_B.pdf">https://www.portseattle.org/sites/default/files/2018-03/T5_FEIS_volume_II_Appx_B.pdf</a></p> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**3. Is there another IUR from the Ramboll paper (or average of some or all of them) (Table 1 of Ramboll Environ's white paper) that you believe is more scientifically sound than CalEPA's IUR for DPM?**

| <b>ATSAC Member:</b> | <b>Response:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe          | At this point in time, there is no DPM IUR contained in the Ramboll white paper that is more appropriate for use by DEQ and OHA to develop a DPM cancer TRV than the OEHHA DPM IUR.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Daisy Dong           | <p>I prefer to select the high end of the IUR of the proposed range (10<sup>-3</sup> - 10<sup>-5</sup>) from Ramboll Environ 2016 white paper, that's to say use the IUR = 1 x 10<sup>-3</sup> per ug/m<sup>3</sup>, which translates to a cancer TRV of 0.001 ug/m<sup>3</sup> for DPM based on the excess risk of 1 in a million. My rationales are listed below:</p> <p>OEHHA's TRV is based on Garshick et al. 1988, which is an old study judged by WHO, EPA, and HEI as inadequate for the development of a quantitative estimate of human risk for cancer. This study also came with many limitations highlighted in DEQ's framing document.</p> <p>Currently there are more recent and better designed studies (Steenland et al., 1998; Silverman et al., 2012; and Garshick et al., 2012) and these studies were considered adequate to derive a quantitative estimate by HEI.</p> <p>Although Crump 2014 and Morfeld and Spallek 2015 criticized the methodology used by Vermeulen et al. 2014, I don't see why these criticisms made the Vermeulen 2014 values less uncertain than OEHHA's IUR based on an old and less robust study. I also think Vermeulen 2014 response made a good argument to dispute some of those criticisms.</p> |
| John Stanek          | Based on the sources of information provided, there is not another more scientifically sound IUR presented in the Ramboll paper. The CalEPA value proposed for selection by DEQ is within both the range of values suggested by Ramboll and the range of values determined in other analyses presented in Table 1. This evaluation taken together with additional discussion concerning uncertainty could further strengthen the rationale for selecting the CalEPA IUR for DPM.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Susan Tilton         | Since DEQ is not developing their own TRV based on these studies, I would recommend comparing your reported TRV to others that have been reported by various methods to show that they are within a similar range or level of protection for public health. This approach will build confidence in the CalEPA IUR developed from the older studies, but is within range of values reported from newer studies using different methods.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| John Vandenberg      | The Ramboll Environ white paper and the DPM Framing Document identify and appropriately summarize the scientific strengths and uncertainties that affect estimation of inhalation unit risk factors from various published studies (except lack of ADAF consideration). Arguments can be presented to support alternative IUR calculations, most notably the Vermeulen (2014) study and response to Crump letter to the editor which conducted a meta-analysis with improved exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>assessment including lag period adjustments. The IUR from Vermeulen (2014) at <math>1.7 \times 10^{-3}</math> is about 6 times more potent than the OEHHA factor of <math>3 \times 10^{-4}</math> ug/m<sup>3</sup> (or, about 4 times more potent based on Vermeulen response to Crump letter to the editor).</p> <p>It is notable that the IUR values shown in Table 1 of the Ramboll Environ white paper are rather similar, despite differences in data and estimate methods employed. This adds confidence that the CalEPA IUR is a scientifically reasonable approach for derivation of TRVs.</p> |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4. What other questions or concerns do you have related either to the proposed DPM cancer TRV or to the DPM Framing Document?

| ATSAC Member:   | Response:                                                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | None noted.                                                                                                                                                                        |
| Daisy Dong      | None except what I indicated above.                                                                                                                                                |
| John Stanek     | As other committee members noted, the application of age-dependent adjustment factors (ADAFs) should be considered and, if warranted, a discussion/rationale provided.             |
| Susan Tilton    | It would be helpful to summarize how the DEQ TRV is derived from the CalEPA IUR. (e.g. reporting the IUR value, cancer slope factor, range of values with 95% confidence interval) |
| John Vandenberg | No additional comments.                                                                                                                                                            |

#### 5. Do you agree with CalEPA's inhalation unit risk DEQ proposes to adopt to calculate a cancer TRV? If not, do you have an alternative suggestion?

| ATSAC Member:   | Response:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| John Budroe     | OEHHA used cancer data from two well-described and well-conducted railroad worker occupational studies (Garshick et al. 1987; 1988) to develop a DPM IUR using appropriate methodology. The OEHHA DPM IUR received multiple rounds of public comments and peer review, and was revised in response to received comments. US EPA has sufficient confidence in the OEHHA DPM IUR that it has listed it in the EPA's Regional Screening Level (RSL) tables for use in Superfund site risk assessment. Additionally, the states of Washington and New Jersey also use the OEHHA DPM IUR as the basis of a diesel exhaust cancer TRV. It would be entirely appropriate for DEQ and OHA to use the OEHHA DPM IUR as the basis for a cancer TRV. |
| Daisy Dong      | See my response to Question 3.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| John Stanek     | Yes, I agree with CalEPA's IUR that DEQ proposes to adopt for calculating cancer TRVs. I do not have an alternative selection.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Susan Tilton    | <ul style="list-style-type: none"> <li>• I support using the CalEPA IUR for deriving the DEQ TRV compared to the proposed alternatives of either deriving a new TRV (not possible due to resources) or not having a cancer TRV (which would limit authority to regulate DPM emissions to reduce public health risk).</li> <li>• This value has been adopted by other states (e.g. Washington DEQ) and is well documented, also follows the standard process of using DEQ authoritative sources</li> <li>• It is important that DEQ/OHA continue to monitor other organizations that generate TRVs and consider new data</li> </ul>                                                                                                        |
| John Vandenberg | I agree with the selection of CalEPA's inhalation unit risk DEQ that proposes to adopt to calculate a cancer TRV for diesel particulate matter. The CalEPA document was based on strong science and underwent extensive peer review. The CalEPA products are considered "authoritative" and I support DEQ and OHA using the CalEPA value which would be consistent with using such assessments as the basis for TRV derivation.                                                                                                                                                                                                                                                                                                           |

## Contact

Oregon Department of Environmental Quality  
Cleaner Air Oregon Program  
[cleanerair@deq.oregon.gov](mailto:cleanerair@deq.oregon.gov)

## Prepared By

This document was prepared by Oregon Department of Environmental Quality and Oregon Health Authority.

Authors:

Holly Dixon, PhD  
Public Health Toxicologist

David Farrer, MS, PhD  
Public Health Toxicologist

Dana Crosby, MPH  
Environmental Health Assessment Program Coordinator



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# **Appendix J: TRV Update and Selection Process: 2023 Process Proposal to ATSAC and OHA Responses**



## Fact Sheet

# Proposed TRV Update and Selection Process for ATSAC Review

## Background

This document summarizes the general process the Department of Environmental Quality (DEQ) and Oregon Health Authority (OHA) propose to follow to update and select inhalation toxicity reference values (TRVs) to use in DEQ's air quality programs. Every three years, the agencies review these values and conduct a rulemaking to update the TRVs. Existing TRVs are in Oregon Administrative Rule (OAR, [340-247-8010 Table 2](#)). Currently, the agencies are preparing for the first triennial TRV review, developing tools to help with the review process, and asking for feedback on the process from the Air Toxics Science Advisory Committee (ATSAC) before we begin searching for specific TRV updates.

Oregon Administrative Rules, adopted by the Environmental Quality Commission, specify sources of toxicity information considered to be authoritative in terms of their scientific rigor and comprehensive methods for producing toxicity information ([OAR 340-247-0030](#)). DEQ uses the term TRV when referring to any similarly derived health-based toxicity value developed by other agencies. A toxic air contaminant could have up to three different TRVs.

- **Chronic cancer TRV** - Air concentration corresponding to a one in one million excess cancer risk, calculated by dividing one in one million (0.000001) by the inhalation unit risk when that air is breathed all the time over a lifetime.
- **Chronic noncancer TRV** - Air concentration below which noncancer health effects are not expected over a year or more of constantly breathing that air.
- **Acute noncancer TRV** - Air concentration below which noncancer health effects are not expected over 24 hours or less from breathing that air.

## Chronic TRV Update and Selection Proposal

The authoritative sources all assume the same exposure time when developing their chronic TRVs. The process to select a TRV from the authoritative sources when more than one TRV is available is not in OAR. In the past, the agencies chose to select the most recently published TRV from among the authoritative sources listed in Table 1 for each toxic air contaminant. For example, the agencies would select a TRV developed in 2018 compared to one developed in 2010. DEQ and OHA propose to use this same selection approach for chronic TRVs in this TRV review. This ensures that the TRVs are based on the most recent review of scientific studies by an authoritative source.

Table 1. Authoritative agencies for selecting chronic TRVs.

700 NE Multnomah Street, Suite 600, Portland, Oregon 97230  
Phone: 503-229-5696, Toll-Free in Oregon: 800-452-4011

| Agency Name                                                   | Name of Chronic TRV                    | Type of TRV Available |
|---------------------------------------------------------------|----------------------------------------|-----------------------|
| U.S. Agency for Toxic Substances and Disease Registry (ATSDR) | Chronic Minimal Risk Level (MRL)       | Noncancer             |
| U.S. Environmental Protection Agency (EPA)                    | Inhalation Unit Risk (IUR)             | Cancer                |
|                                                               | Reference Concentration (RfC)          | Noncancer             |
| California Environmental Protection Agency (CalEPA)           | IUR                                    | Cancer                |
|                                                               | Chronic Reference Exposure Level (REL) | Noncancer             |
| Oregon DEQ in consultation with ATSAC*                        | TRV                                    | Noncancer and Cancer  |

\*“Oregon DEQ in consultation with ATSAC” was added to the list of authoritative sources by the Environmental Quality Commission in 2021. Currently, there are no TRVs from this authoritative source.

## Acute TRV Update and Selection Proposal

Acute TRVs are different because fewer authoritative sources create them and because the authoritative sources make different assumptions about how long people are exposed. DEQ and OHA assume 24 hours of exposure for acute TRVs. In terms of acute TRV application, the Cleaner Air Oregon program is not intended to be a mechanism to address emergency situations where exposures of less than an hour could affect health. There are other mechanisms to address emergency situations caused by very high accidental releases.

In the past, we chose acute TRVs with exposure times that best matched DEQ and OHA’s assumed exposure time of 24 hours. Table 2 shows the authoritative sources listed in order of preference based on how well their TRVs match DEQ and OHA’s assumed 24-hours of exposure.

Table 2. Order of authoritative scientific agencies for acute noncancer TRVs.

| Order of Preference | Agency Name    | Name of Acute TRV | Assumed Exposure Time                 |
|---------------------|----------------|-------------------|---------------------------------------|
| 1                   | U.S. ATSDR     | Acute MRLs        | Less than 2 weeks (includes 24 hours) |
| 2                   | California EPA | Acute RELs        | 1 Hour                                |
| 3                   | U.S. ATSDR     | Intermediate MRLs | 2 weeks to 1 year                     |

DEQ in consultation with ATSAC can also set an acute TRV. This gives us flexibility in choosing and setting acute TRVs that best match our 24-hour exposure duration definition.

There are some existing acute TRVs that are derived from, or are equivalent to, chronic values. This has occurred in two different types of situations:

- When it is not clear when developmental health effects are initiated within the developmental period. Benzo[a]pyrene is an example.
- The acute TRV chosen is a lower value than the chronic TRV. In these cases, we set the acute TRV to be equal to the chronic TRV. Examples include selenium and benzene.

We acknowledge that deriving acute TRVs from chronic TRVs is not ideal and, where appropriate and possible, we would prefer to derive an acute TRV from a study with an acute exposure duration. During our review of acute TRVs, DEQ and OHA will prioritize finding alternative TRVs that are based on studies with short-term/acute exposure periods.

## DEQ in Consultation with ATSAC as an Authoritative Source

Since Oregon DEQ in consultation with ATSAC was added to the list of authoritative sources in 2021 ([OAR 340-247-0030](#)), this gives us more flexibility in the TRV update process. This means that DEQ in consultation with ATSAC can develop TRVs and consider TRVs developed by organizations other than U.S. EPA, U.S. ATSDR, and CalEPA. We primarily rely on these three authoritative sources for TRVs for several reasons:

- **The agencies included in the hierarchy tables go through extensive peer-reviewed processes** to establish TRVs using the best available science and research. For each chemical, these expert panels spend years reviewing hundreds of scientific studies to evaluate the weight of scientific evidence. The evaluations are then shared for public comment. This public process is lengthy and requires substantial investments of tax dollars.
- **Regularly establishing new TRVs is beyond the capacity of agencies in Oregon.** To establish new TRVs, Oregon would have to undergo a rigorous and costly process, like the one mentioned above. Doing this work often is far beyond the current capacity of Oregon agencies. In many instances, the results of a state level review would likely confirm the conclusions of other authoritative sources.
- **Other states rely on agency TRVs** as the basis for health-based industrial toxic air contaminant programs. For example, programs in Washington, New Jersey, Rhode Island, Massachusetts, New Hampshire, New York, Georgia, Minnesota, Michigan, and North Carolina all rely primarily on TRVs from the U.S. EPA and U.S. ATSDR.

Since developing a TRV is very resource intensive, it would be a high bar for us to explore developing a TRV in consultation with ATSAC. It is possible that we might not develop any new TRVs during several different triennial review periods. However, there may be instances where developing a TRV is warranted to protect the health of Oregonians. We predict that we would explore developing our own TRV for a toxic air contaminant if

- None of our other authoritative sources have a toxicity reference value,
- We think the chemical has a high likelihood of harming public health in Oregon,
- There is adequate scientific information available, and
- There is agency staff bandwidth.

In instances where none of the authoritative sources listed in rule have adopted a TRV for a chemical we expect to be posing risk in Oregon, the agencies may also review TRVs developed by other states and countries. This approach still represents a significant effort but is much less resource intensive than developing a new value.

It is important to note that the agencies' current policy (as codified in rule by the authoritative sources listed there) is that they generally agree with policy assumptions those authoritative sources make about how to approach scientific uncertainty and protect health. So, in cases where DEQ and OHA may look at TRVs developed by an organization not on our authoritative source list, they would check that the other organization's assumptions and uncertainty factors are congruent with Oregon's implied policies on addressing scientific uncertainty. DEQ and OHA also expect to consult ATSAC in that type of assessment. At this time, DEQ and OHA anticipate consulting ATSAC on at least two TRVs that meet the criteria discussed above:

- Manganese Acute TRV
- Diesel Particulate Matter Chronic Cancer TRV

The agencies expect to add to and update this list while proceeding with the TRV review process and will share those updates with ATSAC.

## Overall Workflow and Follow Up Meetings with ATSAC

OHA and DEQ toxicologists will check toxicity reference value sources from the US ATSDR, US EPA, and CalEPA for all the existing inhalation TRVs used by DEQ to see if updates need to be made. Staff will also crosscheck the rest of the priority toxic air contaminant list ([OAR 340-247-0040](#) & [OAR 340-247-8010 Table 1](#), the list of chemicals for which industrial facilities must report their emissions to DEQ) to see if there are additional TRVs from the authoritative sources that should be added.

DEQ and OHA will convene an ATSAC meeting when the review process has finished to share which values changed after following our TRV selection process and to gather input on the results. In certain cases, if DEQ and OHA toxicologists propose to deviate from the regular TRV selection process, staff will flag those instances and seek ATSAC input.

For toxic air contaminants that are new to the TRV list or those for which DEQ and OHA propose updated TRVs, staff will also evaluate them for information about developmental or other severe health effects. For more details on this see accompanying primer document on our [HI3 vs. HI5 process](#).

## Discussion Questions for ATSAC Members

1. What questions or feedback do you have on the general process of selecting the most recently published chronic TRV?
2. Do you have questions or feedback on the authoritative source order preference for selecting acute TRVs?
3. Can you recommend other sources of acute TRVs the agencies should consider while prioritizing review of toxic air contaminants where the current acute TRV is equal to the chronic non-cancer TRV or based on chronic studies?
4. What should DEQ and OHA agencies consider when reviewing values from other organizations or agencies not listed as an authoritative source?
5. Do you have questions or comments on the proposed process for reviewing and providing feedback on DEQ's and OHA's work?
6. What other feedback or input do you have for DEQ and OHA?

## Program name and contacts

Cleaner Air Oregon, Oregon Department of Environmental Quality  
Primary Contact: Apollonia (Apple) Goeckner, Program Coordinator  
Alternate Contact: Matt Davis, Program Manager

## Alternate formats

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Oregon Department of Environmental Quality

# Updates to the TRV Update and Selection Process after the ATSAC Meeting on January 20, 2023

This document covers changes made to DEQ's TRV update and selection process following the ATSAC meeting on January 20, 2023. Since that meeting, DEQ and OHA staff have carefully considered the ATSAC's feedback and researched the references that ATSAC members provided. In addition, DEQ and OHA have made changes to the TRV review process, and those changes are detailed in this document.

Before reviewing this document, ATSAC members should read two other related documents:

- Background Document Provided Prior to Meeting #2: [Proposed TRV Update and Selection Process for ATSAC Review](#)
- [Meeting #2 Meeting Minutes](#)

Agency staff will formally begin recording information in the TRV tool for the TRV review process in the next few weeks. Staff anticipate that the full, initial agency review will take several months and will complete that review before planning the next series of ATSAC meetings. If ATSAC members have any follow-up comments or suggestions to the TRV process, please contact Apollonia Goeckner ([apollonia.goeckner@deq.oregon.gov](mailto:apollonia.goeckner@deq.oregon.gov), 503-869-0026).

## Change #1: DEQ will gather additional TRV information to inform TRV selection

DEQ will collect additional detailed information on all TRVs from authoritative sources in the TRV tool and this applies to chronic exposure TRVs, for both cancer and noncancer health effects, and acute exposure TRVs. Prior to the ATSAC meeting, the staff were already planning on recording a variety of information on each TRV into the tool, such as uncertainty factors, TRV publication date, reproductive and developmental hazards, and target organs for noncancer health effects. However, agency staff have since added additional fields into the TRV tool in response to ATSAC comments. Staff will now also enter information on for noncancer TRVs:

- The point of departure (POD) method [e.g., no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), or benchmark concentration (BMC)]
- The author and year of the study used to determine the point of departure
- The factor used to calculate the human equivalent concentration (HEC), if applicable
- The time adjustments used, if applicable

For cancer TRVs, staff will also enter information on the author and year of the study used to calculate the slope factor in addition to TRV publication date.

While these additions will require more staff time during the TRV review process, DEQ agrees with ATSAC members that this information is important to track to make sure the best available TRV is selected and will aid in future ATSAC discussions.

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## Change #2: DEQ will share additional information with the ATSAC

When there are two or more TRVs to choose from for a toxic air contaminant, DEQ will now provide a table of choices to the ATSAC members to review, which will list key differences and similarities between the TRV choices. This table will be presented alongside DEQ's proposed TRV selection. Previously, DEQ had only planned on sharing the proposed TRV selection with ATSAC members.

## Change #3: DEQ will use publication date only as a screening step for chronic exposure TRV selection and use additional information to make proposed TRV selection

DEQ and OHA staff and ATSAC members discussed the process for selecting chronic exposure TRVs for both cancer and noncancer health effects when more than one TRV is available. After that discussion, agency staff are now planning to use TRV published date for screening purposes instead of final section criteria.

The revised plan is that agency staff will first select the most recently published chronic exposure TRV from among the authoritative sources. Staff will then take a close look to see why the most recent TRV may differ from other TRV options. Staff will carefully consider and select a proposed chronic exposure TRV to discuss with ATSAC members using the following list of preferred TRV attributes:

- The TRV includes a new critical study
- The TRV includes modern POD methods (e.g., as indicated by a BMC POD method instead of a LOAEL or NOAEL)
- The TRV includes uncertainty factors (UFs) and/or modifying factors (MFs) informed by new scientific studies when applicable
- The TRV includes factors used to calculate HECs and time adjustments from study conditions to continuous chronic exposure when applicable

DEQ and OHA staff will present the selection choices and the agency proposed TRV to the ATSAC at future meetings.

As suggested by ATSAC members, DEQ and OHA staff may also look at TRVs developed by other state agencies, such as the Texas Commission on Environmental Quality (TCEQ), in certain cases. DEQ agrees with the ATSAC members that stated the importance of only looking at TRVs from organizations that provide transparent TRV derivation documents, offer a public comment process, have similar policies on application of uncertainty and modifying factors, and do not derive their values from occupational exposure limits or non-toxicological endpoints such as odor perception. The original ATSAC fact sheet on the TRV update process describes the conditions when DEQ and OHA would explore adopting a TRV from an organization not listed on the authoritative source list ([pg. 3](#)). For example, agency staff may look for TRVs from alternative sources when no other authoritative sources listed in Oregon Administrative Rule (OAR) have a TRV available.

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## **Change #4: DEQ will use the authoritative source order of preference list as a screening step for acute exposure TRV selection and use additional information to make final proposed TRV selection**

Agency staff plan to use the original DEQ proposal for selecting acute exposure TRVs as a screening tool. Briefly, agency staff will select acute exposure TRVs from the authoritative source list with exposure times that best match DEQ's assumed exposure time of 24 hours (refer to Table 2 of [the original ATSAC fact sheet on the TRV update process](#)). When more than one TRV option is available, staff will carefully consider and select a proposed acute exposure TRV to discuss with ATSAC members using the following list of preferred TRV attributes:

- The TRV is based on studies with exposures that more closely match DEQ's 24-hour acute averaging time
- The TRV includes time adjustments that are appropriate for a 24-hour exposure
- The TRV includes a new critical study
- The TRV includes modern POD methods (e.g., as indicated by a BMC POD method instead of a LOAEL or NOAEL)
- The TRV includes UFs and/or MFs informed by new scientific studies when applicable
- The TRV includes factors used to calculate HECs when applicable

DEQ and OHA will present the selection choices and the agency proposed TRV to the ATSAC at future meetings.

Agency staff will also now check additional sources of acute exposure TRVs that ATSAC members suggested, such as TCEQ, in certain cases. The original ATSAC fact sheet on the TRV update process describes the conditions when DEQ and OHA would explore adopting a TRV from an organization not listed on the authoritative source list ([pg. 3](#)). In agreement with several ATSAC members and the process for selecting chronic exposure TRVs, DEQ plans to only look at acute exposure TRVs from organizations that provide transparent TRV derivation documents, offer a public comment process, and do not derive their values from occupational exposure limits or non-toxicological endpoints such as odor perception.

## **Contact**

Cleaner Air Oregon, Oregon Department of Environmental Quality

Primary Contact: Apollonia (Apple) Goeckner, Program Coordinator

Alternate Contact: Matt Davis, Program Manager

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**Appendix K: Eastern Research Group  
2024 Memorandum on Quality Control  
Process to DEQ and OHA**



# Memorandum

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Date: July 2024

To: J.R. Giska, Apollonia Goeckner, and Susan MacMillan, Oregon Department of Environmental Quality; David Farrer and Holly Dixon, Oregon Health Authority

From: Eastern Research Group, Inc. (ERG)

Subject: QC of Toxicity Reference Values

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## 1. Background

The Oregon Department of Environmental Quality (DEQ) Cleaner Air Oregon program within DEQ's Air Quality Division regulates emissions of Toxic Air Contaminants (TACs) from facilities operating in Oregon based on estimation of related public health risks. As part of the Cleaner Air Oregon program, DEQ and Oregon Health Authority (OHA) periodically review and update the inhalation Toxicity Reference Values (TRVs) used to assess the potential health impacts of facility emissions. DEQ's TRVs are based primarily on reference values published by one or more of four "Authoritative Sources" identified in Oregon Administrative Rule (OAR) 340–247-0030(1). Specifically, DEQ and OHA review TRVs published by U.S. EPA (including both the IRIS and PPRTV programs), California EPA's Office of Environmental Health Hazard Assessment (OEHHA), and U.S. Agency for Toxic Substances and Disease Registry (ATSDR). In addition, DEQ may derive its own TRV in consultation with an Air Toxics Science Advisory Committee (ATSAC).

The Cleaner Air Oregon rules require a triennial review of DEQ's TRVs. In early 2024, DEQ completed its initial review and contracted with Eastern Research Group (ERG) to conduct a Quality Control (QC) review of DEQ's TRV database. Specifically, ERG QC'd data on 327 Toxic Air Contaminants (TACs) housed within the database. The purpose of this QC was to help the Agency reduce the potential for error in the TRV review. ERG conducted this QC from February through May 2024. This memorandum describes the overall approach for the QC and major themes related to the identified errors. A detailed matrix of QC comments and findings for each TAC are attached as an Appendix.

## 2. Approach

On February 8, 2024, DEQ and OHA presented to ERG on the overall TRV rulemaking process and the approach taken by OHA toxicologists to develop the TRV database. As a part of this presentation, OHA demonstrated the TRV tool that ERG would QC and described a workflow document that the toxicologists followed when compiling data for the database. These materials were used by ERG to develop a QC workflow approach.

To ensure consistency and thoroughness when searching reference files and QC'ing the output of the TRV database, ERG internally trained its analysts on a standardized QC protocol. DEQ/OHA provided ERG with a sample batch of TACs to QC. Each batch of TACs was provided as an Excel file with two worksheets per TAC. The primary worksheet was titled "Review of Authoritative Sources". The second worksheet was titled "Target Organ Analysis" (TOA). All ERG analysts QC'd this same sample batch of TACs and resolved

any discrepancies on the QC approach with each other and with DEQ/OHA. For the remaining TACs, ERG would QC the TRVs in batches of approximately 30 TACs and iteratively discuss its findings with DEQ/OHA during weekly meetings.

For each TAC assigned to ERG, the QC review team searched all authoritative sources for inhalation TRVs. In addition, other data elements were cross-checked including units, applicable exposure durations, critical effects, and pertinent derivation information (e.g., time adjustments, uncertainty factors). All QC findings were recorded in an Excel workbook, which included page numbers and direct links to the relevant sources for ease of reference and verification. This Excel compilation is attached as an appendix. If an error was identified that would impact the TRV derivation or was otherwise substantial, a second senior QC reviewer would confirm the finding.

General steps for each phase in the QC review are described below.

**Authoritative Source Search.** ERG reviewers searched each of the three authoritative sources (EPA PPRTV, EPA IRIS, ATSDR, and OEHHA) by CASRN and name for the TAC. Reviewers confirmed accurate retrieval of all inhalation TRVs and that values were converted to the appropriate units, as necessary. The date the TRV was derived and any related comments documented in DEQ's TRV database were also verified for accuracy. This information corresponded to up to 52 information points to check in the Excel file.

**Target Organ Verification.** For every non-cancer TRV from an authoritative source, reviewers verified the number and type of critical effect target organ(s) using the supporting documentation. Each non-cancer TRV had up to 6 information points to check in the primary TRV worksheet, "Review of Authoritative Sources". In addition, reviewers checked the TOA worksheet to confirm the correct endpoints were listed, and that the target organs were consistent with the endpoints.

**DEQ TRVs.** When QC'ing TRVs derived by DEQ, reviewers referred to DEQ's derivation notes to understand the reasoning and any adjustments. Reviewers confirmed the correct dose-response or toxicity values and study information (e.g., exposure continuity, uncertainty factors) were pulled from the alternate source. All DEQ TRVs were recalculated to ensure that the up to 7 information points in the Excel file were accurate.

**TRV Selection and Hierarchy.** After confirming all inhalation TRVs were correctly extracted from every authoritative source, reviewers verified that the TRV selection was consistent with DEQ's stated algorithm for selecting a TRV. Cancer and chronic non-cancer TRVs should align with the most recent source, unless otherwise specified by Agency staff. For acute TRVs, preference is given in the following order: ATSDR acute MRLs, OEHHA acute RELs, or ATSDR intermediate MRLs, unless otherwise specified by Agency staff. A list of preferred TRV attributes that staff considered for TRV selection is described in the DEQ document: [\*Updates to the TRV Update and Selection Process after the ATSAC Meeting on January 20, 2023.\*](#)

**Confirmation of Hazard Index (HI) Designation.** Reviewers searched the U.S. Department of Transportation's (DOT) inhalation hazards list (49 CFR §172.101) by CASRN and name to confirm every TAC's DOT status. If a TAC appeared on the DOT list, reviewers checked whether it had a 6.1 designation with a special provision code between 1 and 6 or a 2.3 designation, ensuring TACs with either of these designations were identified as on the DOT list.

If a TAC was not on the DOT list but reproductive or developmental effects were identified, reviewers verified the endpoints using the documentation from the authoritative source. If a TAC had non-cancer TRVs but no developmental or reproductive effects were identified, reviewers searched across every authoritative source's documentation to ensure no such effects were missed. If a TAC had reproductive or developmental effects, multiple target organs, or was on the DOT list, ERG confirmed the TAC was categorized as HI3. Otherwise, ERG confirmed the TAC was categorized as HI5.

**TOA Worksheet.** Reviewers confirmed there was an entry in the TOA worksheet for every cancer TRV, non-cancer TRV target organ, and any instances where reproductive or developmental effects were pulled from authoritative sources. For each entry, reviewers used the authoritative source's documentation to confirm the following study and derivation information was correctly documented: species, target organ, TRV endpoint, study author and year, uncertainty factors, Point of Departure (POD) method, Human Equivalent Concentration (HEC) adjustments, exposure duration, and time adjustments. If the HEC adjustment factor (e.g., RGDR, DAF) was equal to one, reviewers ensured the HEC status was marked as 'no'. Additionally, reviewers ensured any reproductive or developmental effects following oral exposure were noted as such, and that intermediate exposures were classified as acute. The TOA table for each TAC contained up to 17 information points per TRV, for anywhere from 1 to 8 different TRVs.

### 3. Findings

Out of the 327 TACs reviewed, approximately 111 had a potential error and 106 were updated by DEQ as a result. ERG also classified each error into a 'substantial error' or not by whether it could have impacted the final TRV or HI3/HI5 status. Most of these errors were not substantial (e.g., the date of the authoritative source was not precise). A description of the errors identified within these broader categories is detailed below. A complete summary of QC errors and observations is attached separately as an Excel spreadsheet.

#### 3.1. Substantial errors that potentially impacted final TRVs or HI3/HI5 designation

Below are examples of identified errors that ERG considered to be 'substantial' as they did or could have impacted the final regulatory TRV and HI3/HI5 designation.

**Reproductive and developmental effects:** ERG reviewers identified two TACs, p-nitroaniline and dicyclopentadiene, were misclassified as not having evidence of reproductive or developmental effects. As a result of correcting these errors, the HI designation for these TACs changed from HI5 to HI3.

**Status on the DOT list:** One TAC, sulfuric acid, had an inaccurate DOT list status. However, the HI3/HI5 comment indicated its presence on the DOT list, so this error did not affect its HI3/HI5 designation.

**Number of target organs:** Two TACs, bis(2-chloroethyl) ether and methyl amyl ketone, were incorrectly listed as having more than one target organ for their critical effects. Both of their HI designations changed from HI3 to HI5.

**Authoritative source TRV transcription:** Two TACs had discrepancies in the value of the TRV listed in the database when compared to the authoritative source. Specifically, the IRIS RfC for cerium oxide was not converted to the proper units, and the acute TRV for n-propylbenzene was missing a zero, which resulted in the value being off by an order of magnitude.

**DEQ TRV derivation:** Errors were found in the DEQ TRV derivation for seven TACs. Among these, three TACs (acetone, diethylene glycol monobutyl ether, and diethylene glycol monoethyl ether) had typos in the calculated TRV, although the formulas were correct. One TAC, parathion, was not converted to the proper units. Three of the PAH TACs (7,12-dimethylbenz[a]anthracene, 3-methylcholanthrene, and 5-nitroacenaphthene) had relative potency factors that were not used to calculate DEQ cancer TRVs. This changed the cancer TRV selection for these PAHs.

**Recent updates to authoritative sources:** Two TACs, chloroform and chloroethane, were recently updated by an authoritative source. ATSDR MRLs for chloroform and chloroethane were updated with their profiles in January 2024. As a result, the chronic non-cancer TRV selection for chloroform changed from OEHHA to ATSDR. The acute TRV for chloroethane was updated but the source of the selected TRV did not change.

**TRV source attribution:** One TAC, propylene oxide, attributed the cancer TRV to OEHHA, despite OEHHA adopting IRIS' IUR. The cancer TRV source was updated accordingly for this TAC.

### 3.2. Non-substantial errors that did not impact final TRVs or HI3/HI5 designation

Below are examples identified errors that ERG did not consider to be 'substantial.' These errors were still updated in the TRV database, but they did not have a potential to impact the regulatory TRV or HI3/HI5 designation.

**Authoritative source date:** Errors were identified in the TRV dates from authoritative sources for 64 TACs. This was the most common error. In many cases, these errors were attributed to defaulting to the first of the month as opposed to using the precise day. Overall, none of these errors altered the TRV selection for cancer or chronic non-cancer TRVs.

**Acute or chronic status:** Nine TACs inaccurately classified an endpoint as acute or chronic in the TOA worksheet. The primary reason for these errors was misclassifying reproductive or developmental effects from intermediate exposures as chronic rather than acute.

**Target organs:** Five TACs were found to have errors in their target organ tables, including discrepancies in the count or classification. These errors did not impact HI3/HI5 status. For example, for beryllium and compounds, the number of target organs for the IRIS chronic non-cancer TRV was updated to two from one and made to be consistent with the OEHHA chronic non-cancer TRV, which used the same critical study and effects.

**HEC status:** Three TACs were incorrectly marked 'yes' for having an HEC in the TRV despite the adjustment factor being one. According to DEQ/OHA's protocol this is incorrect. An additional three TACs had errors in the adjustment factor, such as a typo or missing adjustment factor.

**Comment:** Eight TACs had an error or were missing information in a comment field. For example, dichlorvos did not include a comment clarifying why the OEHHA IUR was not extracted. Other examples of comment errors included potency factor typos or missing adjustment factors.

**Missing or outdated TOA entries:** Four TACs were missing entries for critical effects or reproductive/developmental effects in the TOA table. Additionally, two TACs had outdated entries from previous TRV derivations or reproductive/developmental effects that were no longer available.

**Authoritative source TRV transcription:** One TAC had a transcription error from an authoritative source that was ultimately was not selected as the TRV.

**Time adjustments:** For three TACs, either the time adjustment factor was missing or incorrect.

**Exposure duration:** Incorrect exposure durations were identified in seven TACs.

**Study author and year:** Five TACs listed an incorrect study author or year.

**Links to sources:** Six TACs were missing links to supporting documentation from authoritative sources.

#### 4. Conclusion

The QC review conducted by ERG for DEQ/OHA successfully identified and corrected several errors within the DEQ TRV database for TACs, many of which would have impacted the final regulatory TRVs. This QC process ensured that all TRVs were accurately derived, documented, and verified against authoritative sources, thereby improving the reliability and validity of DEQ's TRV database. The comprehensive review and subsequent updates enhance the Cleaner Air Oregon program's ability to regulate TAC emissions based on sound scientific data and protect public health effectively.

#### 5. Appendix

*Attached separately as an Excel file: **ODEQ QA Task 1 Tracking Sheet - Final.xlsx***

**Appendix L: Eastern Research Group  
2024 Memorandum Summarizing  
Published Inhalation Toxicity Values  
on Specific Contaminants to DEQ and  
OHA & Annotated by DEQ and OHA**



# Memorandum [Annotated by DEQ]

Date: July 2024

To: J. R. Giska, Apollonia Goeckner, and Susan MacMillan, Oregon Department of Environmental Quality; David Farrer and Holly Dixon, Oregon Health Authority

From: Eastern Research Group, Inc. (ERG)

Subject: Summaries of Published Inhalation Toxicity Values

## Annotation

The Oregon Department of Environmental Quality (DEQ) has annotated this version of ERG's memorandum addressed to DEQ. The purpose of the annotation is to clarify which of the toxicity reference values (TRVs) researched by ERG DEQ is proposing for use in the DEQ's air quality programs. In many cases, multiple TRV options were described by ERG. These annotations also explain why DEQ selected certain TRVs over others for proposed use in the program.

DEQ's criteria for selection are described here

(<https://www.oregon.gov/deq/aq/Documents/ATSAC-TRVUpdate.pdf>). In

addition to those previously stated criteria, DEQ also preferred TRV candidates that:

1. Had transparent and publicly available derivation information
2. Were not derived from occupational exposure limits
3. Were not derived based on an LC50 or LD50

DEQ's annotations are in this larger, green font. All text not in this font is text from the original memo from ERG to DEQ.

## 1. Background

The Oregon Department of Environmental Quality (DEQ) Cleaner Air Oregon program within DEQ's Air Quality Division regulates emissions of Toxic Air Contaminants (TACs) from facilities operating in Oregon based on estimation of related public health risks. As part of the Cleaner Air Oregon program, DEQ and Oregon Health Authority (OHA) periodically review and update the inhalation Toxicity Reference Values (TRVs) used to assess the potential health impacts of facility emissions. DEQ's TRVs are based primarily on reference values published by one or more of four "Authoritative Sources" identified in Oregon Administrative Rule (OAR) 340-247-0030(1). Specifically, DEQ and OHA review TRVs published by U.S. EPA (including both the IRIS and PPRTV programs), California EPA's Office of Environmental Health Hazard Assessment (OEHHA), and U.S. Agency for Toxic Substances and Disease Registry (ATSDR). In



addition, DEQ may derive its own TRV in consultation with an Air Toxics Science Advisory Committee (ATSAC).

When TRVs are not available from the above Authoritative Sources, DEQ may refer to TRVs from other state or international agencies. Cleaner Air Oregon is currently in the process of updating its TRVs. To assist DEQ and OHA toxicologists, DEQ contracted with Eastern Research Group (ERG) to compile potentially relevant reference values from other agencies for certain TACs. Specifically, ERG was asked to compile and summarize TRVs from all 50 U.S. states, Australia, Canada, the European Union, and the World Health Organization (WHO) for the following TACS:

- 1-methylnaphthalene
- 2-methylnaphthalene
- Copper naphthenate
- 4,5-Dichloro-2-octyl-3(2H)-isothiazolone (DCOI)
- Poly- and perfluoroalkyl substances (PFAS)\*

*\*DEQ/OHA provided ERG with a list of six PFAS: PFBS, PFBA, PFHxS, PFHxA, PFOA, and PFOS. In addition, DEQ/OHA asked ERG to supply a list of additional PFAS with reference values from other governmental agencies. The derivation of this list is documented below.*

This memorandum summarizes results of ERG's compilation of inhalation-based TRVs from state and international agencies.

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### 3. Approach

ERG's approach for compiling inhalation TRVs from other government agencies consisted of several phases, each designed to ensure the thoroughness and accuracy of the compiled information. Details on each phase of the approach are described below.

#### *Initial Compilation of Data Sources*

ERG's public health scientists first assembled a comprehensive list of air toxics data sources. This list consists of state agency air toxics programs (primarily environmental agencies) from all 50 U.S. states as well as relevant agencies from Australia, Canada, the European Union, and the World Health Organization. Links to each agency's relevant air toxics lists were stored in an Excel workbook, so that staff could systematically gather published inhalation toxicity values. A complete list of these government agency websites is found in Appendix A.

#### *Systematic Data Collection*

For each assigned TAC, ERG public health scientists accessed every data source referenced above, searched for the TAC, and extracted relevant inhalation toxicity values. Since ERG was not provided a complete list of PFAS to search for, analysts also searched each list for other PFAS that were not included in DEQ/OHA's initial list (e.g., "GenX") and by searching for potentially relevant text, such as "fluoro". All findings were organized in an Excel workbook, which included the identified reference value with direct links to the source of the information as a reference.

#### *Independent Evaluation and Broad Search*

A senior ERG reviewer independently reviewed the work completed by ERG's public health scientists. This reviewer evaluated the compiled resources and performed a separate check for accuracy against other databases that might also contain state and other agency reference values (e.g., EPA's CompTox Chemicals Dashboard). ERG resolved any discrepancies identified from these secondary sources by double-checking the respective primary sources.

#### *Obtaining Source Materials*

Once a complete list of TRVs was compiled, ERG identified and downloaded technical support documents that contained the derivation of the toxicity values. In certain cases, these documents were not identifiable on public websites or there was uncertainty as to whether the identified information was old or current. In these instances, ERG emailed state agency contacts requesting clarifications and the source of the derived TRV.

#### *Data Synthesis and Report Preparation*

After obtaining the technical documentation for each reference value, ERG extracted relevant information that DEQ typically collects for the TRV derivation process. This information included the critical studies, exposure duration, health endpoint, uncertainty factors, and the overall formula used for the derivation. This information is summarized below in this memorandum.

## 4. Findings

Following a review of all sources identified in Appendix A, ERG identified health-based inhalation TRVs for the TACs of interest from nine different states and the European Chemicals Agency (ECHA). In addition, after the start of this project, DEQ/OHA requested ERG include a summary of the following toxicity reviews:

- a December 1999 toxicity review for DCOI from EPA’s Office of Pesticide Protection (OPP),
- a March 2024 Provisional Peer-Reviewed Toxicity Value (PPRTV) document for 1-methylnaphthalene from EPA’s Office of Research and Development (ORD), and
- a May 2024 Draft Toxicological Profile for 1-methylnaphthalene and 2-methylnaphthalene from ATSDR.

Table 1 summarizes which TACs ERG was able to identify an inhalation-based TRV for and the source of that TRV. A brief description of the types of health-based TRVs follows.

**TABLE 1. SUMMARY OF TACs WITH IDENTIFIED TRVs FROM STATE AND OTHER REGULATORY AGENCIES.**

| State/Agency                                     | MD <sup>a</sup> | MA <sup>b</sup> | MI <sup>c</sup> | MN <sup>d</sup> | NH <sup>e</sup> | NJ <sup>f</sup> | NY <sup>g</sup> | TX <sup>h</sup> | WI <sup>i</sup> | EU <sup>j</sup> | OPP <sup>k</sup> | ATSDR <sup>l</sup> | ORD <sup>m</sup> |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|------------------|--------------------|------------------|
| 1-methylnaphthalene                              | Yes             | --              | Yes             | --              | Yes             | --              | Yes             | Yes             | --              | --              | --               | Yes                | Yes              |
| 2-methylnaphthalene                              | Yes             | Yes             | Yes             | --              | Yes             | --              | Yes             | Yes             | --              | --              | --               | Yes                | --               |
| Copper Naphthenate                               | Yes             | --              | --              | --              | --              | --              | --              | Yes             | --              | Yes             | --               | --                 | --               |
| DCOI                                             | --              | --              | --              | --              | --              | --              | --              | Yes             | --              | --              | Yes              | --                 | --               |
| PFBA                                             | --              | --              | --              | Yes             | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| PFBS                                             | --              | --              | --              | Yes             | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| PFHxA                                            | --              | --              | --              | Yes             | --              | --              | --              | --              | --              | --              | --               | --                 | --               |
| PFHxS                                            | --              | --              | --              | Yes             | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| PFOA                                             | --              | --              | Yes             | Yes             | Yes             | Yes             | Yes             | Yes             | Yes             | --              | --               | --                 | --               |
| PFOS                                             | --              | --              | Yes             | Yes             | --              | Yes             | --              | Yes             | --              | --              | --               | --                 | --               |
| PFOSA                                            | --              | --              | --              | --              | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| PFNA                                             | --              | --              | --              | --              | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| PFDA                                             | --              | --              | --              | --              | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| PFDODA                                           | --              | --              | --              | --              | --              | --              | --              | Yes             | --              | --              | --               | --                 | --               |
| 6:2 FTS                                          | --              | --              | Yes             | --              | --              | --              | --              | --              | --              | Yes             | --               | --                 | --               |
| HFPO-DA (Gen-X)                                  | --              | --              | --              | --              | --              | Yes             | --              | --              | --              | Yes             | --               | --                 | --               |
| PFBE                                             | Yes             | --              | Yes             | --              | --              | --              | --              | --              | --              | Yes             | --               | --                 | --               |
| PFIB                                             | Yes             | --              | Yes             | --              | --              | --              | --              | --              | Yes             | --              | --               | --                 | --               |
| Perfluorobutylethylmethyl<br>ethyldichlorosilane | --              | --              | Yes             | --              | --              | --              | --              | --              | --              | --              | --               | --                 | --               |

<sup>a</sup> Maryland Department of the Environment (MDE) Screening Level – MDE screening levels are ambient benchmarks for toxic air pollutants intended to protect public health. “Public health is protected when the emissions of a facility are less than the maximum allowable emissions or when off-site impact of the premises-wide emissions of each TAP is less than the screening levels for the TAP, as determined by modeling.” Source:

<https://mde.maryland.gov/programs/permits/AirManagementPermits/documents/tap%20reg%20guidance%20doc%2003-21-2016.pdf>

<sup>b</sup> *Massachusetts Department of Environmental Protection (MassDEP) Threshold Effects Exposure Limit (TEL) / Allowable Ambient Limit (AAL)* – MassDEP TELs are based on non-cancer health effects and represents a “concentration intended to protect the general population, including sensitive populations such as children, from adverse health effects over a lifetime of continuous exposure” taking into account that people may be exposed from other sources. “For chemicals that do not pose cancer risks, the AAL is based on the TEL”. Source: <https://www.mass.gov/info-details/massdep-ambient-air-toxics-guidelines>

<sup>c</sup> *Michigan Department of Environment, Great Lakes, and Energy (EGLE) Initial Threshold Screening Level (ITSL) / Initial Risk Screening Level (IRSL) / Secondary Risk Screening Level (SRSL)* – EGLE ITSL’s are health-based screening levels for non-carcinogenic effects of a TAC. The IRSL and SRSL are screening levels for carcinogenic effects. The IRSL “is defined as an increased cancer risk of one in one million ( $10^{-6}$ ),” and the SRSL “is defined as an increased cancer risk of one in one hundred thousand ( $10^{-5}$ ).” If a new source permit applicant cannot meet the IRSL then they can meet the SRSL but must include all sources of the TAC. <https://www.michigan.gov/egle/about/organization/air-quality/air-toxics>

<sup>d</sup> *Minnesota Pollution Control Agency (MPCA) / Minnesota Department of Health (MDH) Health Based Values (HBVs) and Risk Assessment Advice (RAA)* – “MDH currently develops [HBVs] and [RAAs] when there is a need for guidance to evaluate health risks to chemicals in air, often by request of the [MPCA] or other state agencies. HBVs are developed after undergoing a comprehensive chemical review of available toxicity studies. RAA may contain greater uncertainty than HBVs as a result of a less rigorous chemical review or because toxicity information is more limited. MDH also develops RAA on a case-by-case basis for specific conditions or specific sites. It is not appropriate to apply a site-specific RAA to other sites without consulting MDH.”  
<https://www.health.state.mn.us/communities/environment/risk/guidance/air/table.html>

<sup>e</sup> *New Hampshire Department of Environmental Services (NHDES) Ambient Air Limits (AAL)* – NHDES AALs are short-term (24-hour) or long-term (annual) health-based values derived from “threshold limit values, reference concentration limits, and such other generally accepted scientific data as may be available.”  
<https://www.gencourt.state.nh.us/rsa/html/X/125-I/125-I-mrg.htm>

<sup>f</sup> *New Jersey Department of Environmental Protection (NJDEP) Initial Threshold Screening Level / Reference Concentration (RfC)*– NJDEP derived inhalation RfCs for PFOA, PFOS and a screening RfC for GenX based on oral-to-inhalation extrapolation from RfDs. These RfCs are analogous to NJDEP’s Initial Threshold Screening Levels. <https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf>,  
<https://dep.nj.gov/wp-content/uploads/dsr/hfpo-da-genx-tsd.pdf>

<sup>g</sup> *New York State Department of Environmental Conservation (DEC) Short-Term Guideline Concentrations (SGC) and Annual Guideline Concentrations (AGC)* –AGCs are developed to protect the public health from the effects associated with long-term continuous, exposure to a contaminant. SGCs represent acute exposures on a one-hour basis. [https://extapps.dec.ny.gov/docs/air\\_pdf/dar1.pdf](https://extapps.dec.ny.gov/docs/air_pdf/dar1.pdf)

<sup>h</sup> *Texas Commission on Environmental Quality (TCEQ) Effects Screening Levels (ESLs), Inhalation Reference Values (ReVs), and RfCs* – TCEQ develops ESLs for air permitting. “ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, the potential for odors to be a nuisance, and effects on vegetation, while long-term ESLs are based on data concerning chronic health and vegetation effects.” The ESLs are screening levels. ReVs are used for air monitoring. “The ReV is a health-protective air concentration,



developed for chemicals with thresholds.” “The ReV is used for air monitoring whereas the health-based ESL, which is 70% lower than the ReV, is used in air permitting.”

“If predicted or measured airborne levels of a constituent do not exceed the screening level, adverse health or welfare effects would not be expected to result. If ambient levels of constituents in air exceed the screening level, it does not necessarily indicate a problem, but a more in-depth review is conducted.” TCEQ has not set ReVs for the TACs described in this memo. TCEQ has also developed inhalation RfCs for select PFAS. <https://www.tceq.texas.gov/downloads/toxicology/esl/special-notations.pdf>, [https://www.tceq.texas.gov/downloads/toxicology/monitoring/amcv/esls\\_amcvs.pdf](https://www.tceq.texas.gov/downloads/toxicology/monitoring/amcv/esls_amcvs.pdf), [https://www.tceq.texas.gov/toxicology/dsd/dsds\\_about](https://www.tceq.texas.gov/toxicology/dsd/dsds_about), <https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf>

<sup>i</sup> Wisconsin Department of Natural Resources (WDNR) Ambient Air Standard – WDNR sets ambient air standards for hazardous air pollutants based on short-term or annual health-based thresholds “protect people from air emissions that are known or suspected to cause cancer or other serious health problems.” <https://widnr.widen.net/view/pdf/n90lmcldhw9/AM405.pdf?t.download=true>, [https://docs.legis.wisconsin.gov/code/admin\\_code/nr/400/445.pdf#page=5](https://docs.legis.wisconsin.gov/code/admin_code/nr/400/445.pdf#page=5)

<sup>j</sup> European Union’s (EUs) European Chemicals Agency (ECHA) Derived No-Effect Level (DNEL) – As a part of the EU’s Registration, Evaluation, Authorisation, and Restriction of Chemical (REACH) regulation, chemical registrants need to provide chemical safety assessments for substances that are imported in a certain quantity. If a chemical has a threshold effect then a DNEL needs to be calculated representing “the level of exposure above which humans should not be exposed”, and these can be based on worker or general population and short or long-term duration. <https://academic.oup.com/annweh/article/59/4/416/2195991>

<sup>k</sup> EPA Office of Pesticide Programs (OPP) Health Effects Division developed a memorandum for DCOI that identified RfDs and toxicological endpoints for inhalation for occupational exposure risk assessments. <https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/128101/128101-034.pdf>

<sup>l</sup> Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRL) – “An estimate of daily human exposure to a hazardous substances that is likely to be without an appreciable risk of adverse non-cancer health effects over a specified route and duration of exposure”. Inhalation MRLs can be derived for acute, intermediate, and chronic exposures. <https://www.atsdr.cdc.gov/mrls/index.html>

<sup>m</sup> EPA Office of Research and Development (ORD) PPRTVs – “A toxicity derivation.” value primarily derived for use in EPA’s Superfund Program. PPRTVs are derived from a review of the relevant scientific literature using EPA methods, sources of data and guidance for value <https://www.epa.gov/pprtv>

The following sections of the memo contain tables that list the TRV options researched and collected by ERG. Rows shaded green in these tables signify the TRVs that DEQ selected for proposed use in DEQ’s air quality programs.



#### 4.1. 1-methylnaphthalene (CAS 90-12-0)

ERG identified both carcinogenic and non-carcinogenic inhalation TRVs for 1-methylnaphthalene from five different state agencies, ATSDR, and EPA. The identified values range from 0.003  $\mu\text{g}/\text{m}^3$  to 250  $\mu\text{g}/\text{m}^3$ . Table 2 summarizes the identified TRVs for 1-methylnaphthalene.

Developmental or reproductive effects were not identified in any of the reviewed state TRV documentation nor in ATSDR's Toxicological Profile.

1-methylnaphthalene is not present on the Department of Transportation (DOT) list of inhalation hazards.

**TABLE 2. INHALATION TRVs FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)**

| State/Agency      | TRV Type                | TRV Value                     | Classification           | DEQ Notes                                                |
|-------------------|-------------------------|-------------------------------|--------------------------|----------------------------------------------------------|
| Maryland DE       | 8-hour* Screening Level | 2.91 $\mu\text{g}/\text{m}^3$ | Non-cancer, chronic      | Derived from Occupational                                |
| Michigan EGL      | Annual ITSL             | 250 $\mu\text{g}/\text{m}^3$  | Non-cancer, chronic      | Older than selected non-cancer, chronic value            |
|                   | Annual IRSL             | 0.14 $\mu\text{g}/\text{m}^3$ | Cancer                   | Unmodified                                               |
|                   | Annual SRSL             | 1.4 $\mu\text{g}/\text{m}^3$  | Cancer                   | Older than selected acute value                          |
| New Hampshire DES | 24-hr AAL               | 15 $\mu\text{g}/\text{m}^3$   | Non-cancer, acute        | Derived from Occupational                                |
|                   | Annual AAL              | 9.7 $\mu\text{g}/\text{m}^3$  | Non-cancer, chronic      | Derived from Occupational                                |
| New York DEC      | Annual AGC              | 7.1 $\mu\text{g}/\text{m}^3$  | Non-cancer, chronic      | Derived from Occupational                                |
| Texas TCEQ        | Short-term ESL          | 200 $\mu\text{g}/\text{m}^3$  | Non-cancer, acute        | Derived from Occupational                                |
|                   | Long-term ESL           | 20 $\mu\text{g}/\text{m}^3$   | Non-cancer, chronic      | Derived from Occupational                                |
| ATSDR             | MRL                     | 0.5 $\mu\text{g}/\text{m}^3$  | Non-cancer, intermediate | Modified to eliminate days/week adjustment for acute TRV |
| EPA ORD PPRTV     | Sub-chronic p-RfC       | .03 $\mu\text{g}/\text{m}^3$  | Non-cancer, sub-chronic  | Doesn't match any categories for CAO TRVs                |
|                   | Chronic p-RfC           | .003 $\mu\text{g}/\text{m}^3$ | Non-cancer, chronic      | Unmodified                                               |

\*Calculated from an occupational exposure limit that assumes an 8-hour workday and a 40-hour workweek

#### 4.1.1. Maryland DE

**TABLE 3. MARYLAND DE 8-HOUR SCREENING LEVEL FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)**

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                                                                           | Comment                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 8-hour Screening Level                                                                                         | 2.91 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                          | Non-carcinogenic, 8-hour screening level. Calculated from a TLV-TWA, “for a conventional 8-hour workday and a 40-hour workweek” |
| Date                                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                              | Calculated from an ACGIH TLV-TWA but year/date not provided.                                                                    |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit                                                                                                                                                                                                                                                                                                                                                                                                     | Calculated from an ACGIH TLV.                                                                                                   |
| Critical study                                                                                                 | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Species                                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Target Organ                                                                                                   | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Uncertainty Factors                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| POD Method                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Human Equivalent Concentration in TRV?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Duration of exposure                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Time Adjustment in TRV?                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Developmental or Reproductive Effects?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Oral to inhalation extrapolation?                                                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Additional notes                                                                                               | <p>ERG reached out to Maryland DE to obtain the Agency’s current TRV values and their derivations. MDE responded by noting that the TRV was set by the ACGIH TLV. Other information was not provided.</p> <p>According to regulation: “If a toxic air pollutant (TAP) has a threshold limit value-time weighted average (TLV-TWA), divide the TLV-TWA by 100 to calculate an 8-hour time-weighted average screening level”.</p> |                                                                                                                                 |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx">https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx</a><br><br><a href="https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03">https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03</a><br><br>(see email from MDE). |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.1.2. Michigan EGL

TABLE 4. MICHIGAN EGLE ITSL FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                             | Comment                                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ITSL                                                                                                           | 250 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                             | Non-carcinogenic, annual screening level                                                                                                                                      |
| Date                                                                                                           | January 12, 2017                                                                                                                                                                                                                                                                                                                  | Originally derived on April 28, 2008, but updated the averaging time from the regulatory default of 24 hours to annual on January 12, 2017.                                   |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Derived from a chronic oral mouse study.                                                                                                                                                                                                                                                                                          | --                                                                                                                                                                            |
| Critical study                                                                                                 | Murata Y, Denda A, Maruyama H, and Konishi Y. 1993. Chronic Toxicity and Carcinogenicity Studies of 1-Methylnaphthalene in B6C3F1 Mice. Fund Appl Toxicol 21:44-51. <a href="https://www.sciencedirect.com/science/article/abs/pii/S0272059083710705">https://www.sciencedirect.com/science/article/abs/pii/S0272059083710705</a> | Chronic oral mouse study. Same as used for IRSL/SRSL and by ATSDR to develop chronic <i>oral</i> MRL.                                                                         |
| Species                                                                                                        | Mouse                                                                                                                                                                                                                                                                                                                             | --                                                                                                                                                                            |
| Target Organ                                                                                                   | Respiratory system                                                                                                                                                                                                                                                                                                                | And other (organ weights and hematology)                                                                                                                                      |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Pulmonary alveolar proteinosis, and changes in organ weights and hematology                                                                                                                                                                                                                                                       | Effects occurred at lowest dose of 71 mg/kg/day.                                                                                                                              |
| Other Endpoints                                                                                                | Peripheral blood changes including increased hemoglobin, mean corpuscular hemoglobin, albumin/globulin ratio, as well as significant organ weight changes for the brain, heart and thymus.                                                                                                                                        | Male mice had a slight statistically increased incidence of alveolar/bronchiolar adenomas and adenocarcinomas. This cancer effect is used as the basis for the IRSL and SRSL. |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Uncertainty Factors                    | Total UF = 1000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | UF (sensitive individuals) = 10<br>UF (animal to human) = 10<br>UF (LOAEL to NOAEL) = 10                                                                                                                                                                                                                                                                                                                                                          |
| POD Method                             | LOAEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | RfD = 71 mg/kg/day / 1000 = 71 µg/kg/day, which is identical to ATSDR's chronic oral MRL based on the same study.                                                                                                                                                                                                                                                                                                                                 |
| Human Equivalent Concentration in TRV? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | --                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Duration of exposure                   | 81 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ITSL originally assumed as 24 hour averaging time, but updated to annual based on 81 weeks.                                                                                                                                                                                                                                                                                                                                                       |
| Time Adjustment in TRV?                | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | (see notes below)                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Developmental or Reproductive Effects? | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | No mention of reproductive or developmental effects in TRV source document.                                                                                                                                                                                                                                                                                                                                                                       |
| Oral to inhalation extrapolation?      | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Chronic ITSL calculated based on approach in <a href="#">R232(1)(b)</a> , which assumes a person breathing 20 m <sup>3</sup> a day and weighing 70 kg. ITSL = 71 µg/kg/day x (70kg/(20m <sup>3</sup> /day)) = 248 µg/m <sup>3</sup> rounded to 250 µg/m <sup>3</sup> . Originally this was applied to the statutory default of a 24hr averaging time, but this was then updated to apply to an annual averaging without changing the calculation. |
| Additional notes                       | <p>In 2017 EGLE changed this TRV from applying to a 24-hour averaging time to an annual averaging time without changing the value of the TRV itself, so there was not a formal time adjustment in the calculation:</p> <p>“The averaging time (AT) assigned at that time was 24 hours, as per the default methodology (Rule 232(2)(b)). The current file review concludes that the AT may appropriately be set at annual, as the screening level is based on an 81 week feeding study in mice (Murata et al. 1993). Therefore, the AT is being changed from 24 hours to annual at this time.”</p>                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Links to TRV Sources                   | <p><a href="https://www.michigan.gov/egle/-/media/Project/Websites/egle/Documents/Programs/AQD/toxics/screening-levels-alphabetical.pdf">https://www.michigan.gov/egle/-/media/Project/Websites/egle/Documents/Programs/AQD/toxics/screening-levels-alphabetical.pdf</a></p> <p><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/90-12-0/90-12-0_annual_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/90-12-0/90-12-0_annual_ITSL.pdf</a></p> <p><a href="https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level">https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level</a></p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

TABLE 5. MICHIGAN EGLE IRSL/SRSL FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                 | Comment                                                                                                             |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| IRSL                                                                                                           | 0.14 µg/m <sup>3</sup> annual                                                                                                                                                                                                                                                                                                         | IRSL based on increased cancer risk of one in one million (10 <sup>-6</sup> ).                                      |
| SRSL                                                                                                           | 1.4 µg/m <sup>3</sup> annual                                                                                                                                                                                                                                                                                                          | SRSL based on increased cancer risk of one in one hundred thousand (10 <sup>-5</sup> ).                             |
| Date                                                                                                           | April 28, 2008                                                                                                                                                                                                                                                                                                                        | Originally derived on April 28, 2008. The ITSL was updated on January 12, 2017, but the IRSL/SRSL were not changed. |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Derived from a chronic oral mouse study.                                                                                                                                                                                                                                                                                              | --                                                                                                                  |
| Critical study                                                                                                 | Murata Y, Denda A, Maruyama H, and Konishi Y. 1993. Chronic Toxicity and Carcinogenicity Studies of 1-Methyl-naphthalene in B6C3F1 Mice. Fund Appl Toxicol 21:44-51.<br><a href="https://www.sciencedirect.com/science/article/abs/pii/S0272059083710705">https://www.sciencedirect.com/science/article/abs/pii/S0272059083710705</a> | Chronic oral mouse study. Same as used for ITSL and by ATSDR to develop chronic oral MRL.                           |
| Species                                                                                                        | Mouse                                                                                                                                                                                                                                                                                                                                 | --                                                                                                                  |
| Target Organ / Effect                                                                                          | Cancer                                                                                                                                                                                                                                                                                                                                | --                                                                                                                  |
| Description of TRV endpoints/basis for points of departure (POD)                                               | Increased incidence of alveolar/bronchiolar adenomas and adenocarcinomas in male mice                                                                                                                                                                                                                                                 | A "slight, statistically significant" increase in incidence in Male mice.                                           |
| Other Endpoints                                                                                                | Peripheral blood changes including increased hemoglobin, mean corpuscular hemoglobin, albumin/globulin ratio, as well as significant organ weight changes for the brain, heart and thymus.                                                                                                                                            | These non-cancer effects are used as the basis for the ITSL.                                                        |
| Uncertainty Factors                                                                                            | --                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                  |
| POD Method                                                                                                     | --                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                  |
| Human Equivalent Concentration in TRV?                                                                         | Yes                                                                                                                                                                                                                                                                                                                                   | See additional notes below.                                                                                         |
| Duration of exposure                                                                                           | 81 weeks                                                                                                                                                                                                                                                                                                                              | --                                                                                                                  |
| Time Adjustment in TRV?                                                                                        | --                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                  |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                             |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Oral to inhalation extrapolation | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | See additional notes below. |
| Additional notes                 | <p>“The BMDS multistage - cancer model can be used to calculate the male mouse oral potency of <math>3.63 \times 10^{-3} \text{ (mg/kg)}^{-1}</math>, which can be converted to the human oral potency of <math>2.33 \times 10^2 \text{ (mg/kg)}^{-1}</math> by using body weight adjustment to the 3/4 power. The inhalation cancer potency can then be determined by converting the oral potency to the human inhalation potency of <math>6.7 \times 10^{-6} \text{ (}\mu\text{g/m}^3\text{)}^{-1}</math> based on a 70 kg person breathing <math>20 \text{ m}^3</math> a day. This inhalation potency will result in the IRSL being <math>0.14 \text{ }\mu\text{g/m}^3</math> and the SRSL being <math>1.4 \text{ }\mu\text{g/m}^3</math> with annual averaging.”</p>                                                                                                                                     |                             |
| Links to TRV Sources             | <p><a href="https://www.michigan.gov/egle/-/media/Project/Websites/egle/Documents/Programs/AQD/toxics/screening-levels-alphabetical.pdf">https://www.michigan.gov/egle/-/media/Project/Websites/egle/Documents/Programs/AQD/toxics/screening-levels-alphabetical.pdf</a></p> <p><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/90-12-0/90-12-0_annual_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/90-12-0/90-12-0_annual_ITSL.pdf</a></p> <p><a href="https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361231-cancer-risk-assessment-screening-methodology">https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361231-cancer-risk-assessment-screening-methodology</a></p> |                             |

#### 4.1.3. New Hampshire DES

TABLE 6. NEW HAMPSHIRE DES AAL FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)

| Variable                                                                                                       | Value                                                                               | Comment                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24-Hour AAL                                                                                                    | $15 \text{ }\mu\text{g/m}^3$                                                        | 24-hour ambient air limit                                                                                                                                                                                                                                                                                           |
| Annual AAL                                                                                                     | $9.7 \text{ }\mu\text{g/m}^3$                                                       | Annual ambient air limit                                                                                                                                                                                                                                                                                            |
| Date                                                                                                           | November 11, 2009                                                                   | Based on date regulation was amended to add 1-Methylnaphthalene:<br><a href="https://www.des.nh.gov/sites/g/files/ehbemt341/files/inline-documents/2022-03/AnnualToxListUpdate-2000to2022.pdf">https://www.des.nh.gov/sites/g/files/ehbemt341/files/inline-documents/2022-03/AnnualToxListUpdate-2000to2022.pdf</a> |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit modified with toxicity data from an oral toxicity study | Regulatory approach calls for setting the AAL based on modifying the ACGIH value based on other available toxicity data. See additional notes below.                                                                                                                                                                |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | <ol style="list-style-type: none"> <li>1) ACGIH OEL,</li> <li>2) Dangerous Properties of Industrial Materials, N. Irving Sax. page 2268 (1996), cited in the Hazardous Substances Data Bank (HSDB), and</li> <li>3) DHHS/ATSDR; Toxicological Profile for Naphthalene, 1-Methylnaphthalene, 2-Methylnaphthalene p. 37, 39, 44 (1995). Cited in HSDB</li> </ol> | ACGIH is used as basis of AAL, and the other two studies are used to determine acute and chronic toxicity values to set a 'Toxicity Factor' and 'Time Adjustment Factor' to modify the ACGIH value according to the regulatory formula. (See additional notes below) |
| Species                                                           | Rat, Mice                                                                                                                                                                                                                                                                                                                                                      | Rat study was used to determine acute toxicity and Mice study was used for chronic toxicity.                                                                                                                                                                         |
| Target Organ                                                      | --                                                                                                                                                                                                                                                                                                                                                             | See comment in 'Description of TRV endpoints'                                                                                                                                                                                                                        |
| Description of TRV endpoints/ basis for points of departure (POD) | --                                                                                                                                                                                                                                                                                                                                                             | The underlying source for the old ACGIH OEL value used is not available. Death (LD50) was the endpoint in the acute rat study. Hematological changes were observed in the chronic mice study.                                                                        |
| Other Endpoints                                                   | --                                                                                                                                                                                                                                                                                                                                                             | --                                                                                                                                                                                                                                                                   |
| Uncertainty Factors                                               | <p>NH DES refers to a 'Safety Factor (SF)' of 71.</p> <p>A time adjustment factor is also applied of 4.2 for the annual AAL and 2.8 for the 24-hour AAL. (See below).</p>                                                                                                                                                                                      | New Hampshire assigned 1-methylnaphthalene a 'Toxicity Factor (TF)' designation of Class II based on acute and chronic toxicity studies. A Class II TF corresponds to a 'Safety Factor (SF)' of 71.                                                                  |
| POD Method                                                        | OEL                                                                                                                                                                                                                                                                                                                                                            | OEL = 2900 µg/m <sup>3</sup>                                                                                                                                                                                                                                         |
| Human Equivalent Concentration in TRV?                            | --                                                                                                                                                                                                                                                                                                                                                             | Not explicit in calculation from OEL.                                                                                                                                                                                                                                |
| Duration of exposure                                              | --                                                                                                                                                                                                                                                                                                                                                             | Varies by study.                                                                                                                                                                                                                                                     |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                              |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Time Adjustment in TRV?                | <p>Yes</p> <p>For the Annual AAL, NHDES adjusted the OEL by a factor of <math>4.2 = 24 \text{ hrs per day} / 8 \text{ hrs per work day} * (7 \text{ days per week} / 5 \text{ days work week})</math></p> <p>For the 24-hour AAL, NHDES assigned 1-methylnaphthalene a 'Time Adjustment Factor (TAF)' based on regulatory criteria 'D,' which corresponds to a TAF of 2.8.</p>                                                                                                                                                                                                                                                                                                                                                                                                                       | See formulas in 'additional notes' below.                    |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | No mention of developmental or reproductive effects/studies. |
| Oral to inhalation extrapolation       | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Not explicit in calculation of TRV from OEL.                 |
| Additional notes                       | <p>Calculation of AALs are shown below:</p> <p><u>Annual AAL</u></p> $= \text{OEL} / (4.2 * \text{SF})$ $= 2900 \mu\text{g}/\text{m}^3 / (4.2 * 71)$ $= 2900 \mu\text{g}/\text{m}^3 / 298.2$ $= 9.73 \mu\text{g}/\text{m}^3$ <p>Where: <math>4.2 = (24 \text{ hrs per day} / 8 \text{ hrs per work day}) * (7 \text{ days per week} / 5 \text{ days work week})</math>.</p> <p><u>24-hour AAL</u></p> $= \text{OEL} / (\text{SF} * \text{TAF})$ $= 2900 \mu\text{g}/\text{m}^3 / (71 * 2.8)$ $= 2900 \mu\text{g}/\text{m}^3 / (198.8)$ $= 14.6 \mu\text{g}/\text{m}^3$ <p>Note the ACGIH OEL of <math>2,900 \mu\text{g}/\text{m}^3</math> appears outdated as the current ACGIH Threshold Limit Value (TLV) is <math>0.3 \text{ mg}/\text{m}^3</math> (<math>300 \mu\text{g}/\text{m}^3</math>).</p> |                                                              |
| Links to TRV Sources                   | <p><a href="https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance">https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance</a></p> <p><a href="https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/env-a-1400.pdf">https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/env-a-1400.pdf</a></p> <p>See email from New Hampshire DES for documentation of derivation.</p>                                                                                                                                                                                                                                                                                                                                                                               |                                                              |



#### 4.1.4. New York DEC

TABLE 7. NEW YORK DEC AGC FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)

| Variable                                                                                                       | Value                                                                                                                                                                                             | Comment                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| AGC                                                                                                            | 7.1 µg/m <sup>3</sup>                                                                                                                                                                             | Annual Guideline Concentration                                                                                                   |
| Date                                                                                                           | February 12, 2021                                                                                                                                                                                 | Date of Issue for: <a href="#">“Guidelines for the Evaluation and Control of Ambient Air Contaminants Under 6NYCRR Part 212”</a> |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational exposure limit                                                                                                                                                                       | Based on 2018 ACGIH’s TLV-TWAs                                                                                                   |
| Critical study                                                                                                 | American Conference of Governmental Industrial Hygienists (ACGIH) 2018. Documentation of Threshold Limit Values and Biological Exposure Indices, 7th Edition – 2015 Supplement. Cincinnati, Ohio. | The 2018 ACGIH TLV used by NYDEC appears to be the same as the current TLV (300 µg/m <sup>3</sup> ).                             |
| Species                                                                                                        | Rat, Mice                                                                                                                                                                                         | Based on current ACGIH documentation.                                                                                            |
| Target Organ                                                                                                   | Respiratory tract, Lung, Liver                                                                                                                                                                    | Based on current ACGIH documentation.                                                                                            |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Upper respiratory tract irritation, lung damage, liver effects                                                                                                                                    | Based on current ACGIH documentation.                                                                                            |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                | Other studies reference skin and eye irritation in ACGIH documentation.                                                          |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Uncertainty Factors                    | UF of 42 (inferred).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <p>The UF is defined in regulation by the ‘toxicity level’, which can be High, Moderate, or Low. The UF is 420 for Medium or High toxicity substances and 42 for Low toxicity substances. (See additional notes).</p> <p>No toxicity level is explicitly defined by NYDOH for 1-methylnaphthalene; however, based on the current ACGIH value of 300 µg/m<sup>3</sup>, and uncertainty factor of 42 is likely used to derive the AGC of 7.1 µg/m<sup>3</sup>.</p> |
| POD Method                             | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Unclear POD method for ACGIH derivation.                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Human Equivalent Concentration in TRV? | Not explicit in NYDE calculation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Unclear on human equivalent concentration used in ACGIH derivation.                                                                                                                                                                                                                                                                                                                                                                                              |
| Duration of exposure                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Unclear on duration of exposure from ACGIH derivation.                                                                                                                                                                                                                                                                                                                                                                                                           |
| Time Adjustment in TRV?                | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | The uncertainty factors are based on adjusting the 8-hr work day exposure to a 24-hr exposure and a 5-day work week to 7-day exposure.                                                                                                                                                                                                                                                                                                                           |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | No developmental or reproductive effects listed in current ACGIH documentation.                                                                                                                                                                                                                                                                                                                                                                                  |
| Oral to inhalation extrapolation       | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Additional notes                       | <p>“AGCs are calculated by starting with the TLV for an air contaminant and adjusting it by an uncertainty factor. The uncertainty factor for a chemical classified as HIGH or MODERATE toxicity is 420. The uncertainty factor for a chemical classified as LOW toxicity is 42. The uncertainty factors are based on adjusting the 8-hr work day exposure to a 24-hr exposure and a 5-day work week to 7-day exposure, and by applying an additional factor of 10 for LOW toxicity or 100 for MODERATE and HIGH toxicity contaminants to compensate for applying an occupational standard to the general population.”</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Links to TRV Sources                   | <p><a href="https://dec.ny.gov/environmental-protection/air-quality/controlling-pollution-from-facilities/air-toxics-program">https://dec.ny.gov/environmental-protection/air-quality/controlling-pollution-from-facilities/air-toxics-program</a></p> <p><a href="https://dec.ny.gov/docs/air_pdf/dar1.pdf">https://dec.ny.gov/docs/air_pdf/dar1.pdf</a></p>                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

#### 4.1.5. Texas TCEQ

TABLE 8. TEXAS TCEQ SHORT AND LONG-TERM ESLs FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Comment                                                 |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Short-Term ESL                                                                                                 | 200 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Short-Term defined as one hour                          |
| Long-Term ESL                                                                                                  | 20 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Long-Term defined as 70 years                           |
| Date                                                                                                           | November 17, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                         |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit (OEL)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | TRV derived from “Russia OEL” of 20 mg/m <sup>3</sup> . |
| Critical study                                                                                                 | Russian OEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Original source of Russia OEL was not available.        |
| Species                                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Target Organ                                                                                                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Uncertainty Factors                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| POD Method                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Human Equivalent Concentration in TRV?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Duration of exposure                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Time Adjustment in TRV?                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                      |
| Developmental or Reproductive Effects?                                                                         | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | No mention of developmental or reproductive studies.    |
| Oral to inhalation extrapolation                                                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                         |
| Additional notes                                                                                               | <p>Values are “Interim.” which “indicates that the ESL is current and will be reviewed by the Toxicology Division at a later date. Also, interim ESLs may be updated pending the release of updated toxicity information or odor data.”</p> <p>Same source and values as 2-methylnaphthalene. The TRV documentation has the following note:</p> <p>“ATSDR groups naphthalene and 1- and 2-methylnaphthalene together in it's Tox Profile, no inhalation data is available for 1-methylnaphthalene, but LD50 is much higher than for naphthalene, surrogating would raise ESLs significantly, ACGIH based it's values on an RD50, which does not follow with the TCEQ guidelines, to be conservative, use Russia's OEL to calculate ESLs.”</p> |                                                         |
| Links to TRV Sources                                                                                           | <p>TAMIS database -&gt; Start Report -&gt; Tox Document Report -&gt; Next -&gt; Create Report for CAS number 90-12-0:<br/> <a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a> </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                         |

#### 4.1.6. ATSDR

TABLE 9. ATSDR MRL FOR 1-METHYLNAPHTHALENE (CAS 90-12-0)

| Variable                                                                                                       | Value                                                                                                                                                                                                              | Comment                                                                                                                                               |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| MRL                                                                                                            | $9 \times 10^{-5}$ ppm ( $0.5 \mu\text{g}/\text{m}^3$ )                                                                                                                                                            | Provisional intermediate exposure MRL                                                                                                                 |
| Date                                                                                                           | May 2024                                                                                                                                                                                                           | Updated draft Tox Profile released over the course of this project.                                                                                   |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Inhalation toxicity study                                                                                                                                                                                          | --                                                                                                                                                    |
| Critical study                                                                                                 | Kim YS, Lee MJ, Seo DS, Kim TH, Kim MH, Lim CH. Thirteen-week inhalation toxicity study of 1-methylnaphthalene in F344 rats. Toxicol Res. 2019 Nov 26;36(1):13-20. doi: 10.1007/s43188-019-00009-1.                | Same study as PPRTV RfCs<br><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6990237/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6990237/</a> |
| Species                                                                                                        | Rat                                                                                                                                                                                                                | --                                                                                                                                                    |
| Target Organ / Effect                                                                                          | Respiratory tract                                                                                                                                                                                                  | --                                                                                                                                                    |
| Description of TRV endpoints/basis for points of departure (POD)                                               | Nasal mucous cell hyperplasia                                                                                                                                                                                      | --                                                                                                                                                    |
| Other Endpoints                                                                                                | Significant increase in activated partial thromboplastin time (APTT) and prothrombin time (PT); significant serum increases of albumin (4%) and sodium (1%); transitional epithelial cell hyperplasia (males only) | --                                                                                                                                                    |
| Uncertainty Factors                                                                                            | UF = $3 \times 10 = 30$                                                                                                                                                                                            | UF (animal to human) = 3<br>UF (sensitive individuals) = 10                                                                                           |
| POD Method                                                                                                     | BMCL <sub>HEC</sub>                                                                                                                                                                                                | BMCL <sub>10</sub> = 0.06 ppm<br>BMCL <sub>HEC</sub> = 0.0027 ppm                                                                                     |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | <p>“The critical effects of 1-methylnaphthalene were nasal lesions, therefore, the BMCL10ADJ was converted to a HEC by multiplying the BMCL10 by the rat-specific regional gas dose ratio that corresponds with the extrathoracic region (RGDRET). This RGDRET is calculated using the following equation as defined by EPA (1994):”</p> $RGDRET = (V_{Ea} / SA_a) / (V_{Eh} / SA_h)$ $= (0.254/15) / (13.8/200) = 0.25$ $BMCL_{HEC} = BMCL_{10ADJ} \times RGDRET = 0.011\text{ppm} \times 0.25 = 0.0027\text{ppm}$ | <p>RGDRET = Rat-specific regional gas dose ratio that corresponds with the extrathoracic region</p> <p><math>V_{Ea}</math> = ventilation rate for male F344 rats = 0.254 L/minute (EPA 2012)</p> <p><math>V_{Eh}</math> = ventilation rate for humans = 13.8 L/minute (EPA 1994)</p> <p><math>SA_a</math> = surface area of the extrathoracic region in rats = 15 cm<sup>2</sup> (EPA 1994)</p> <p><math>SA_h</math> = surface area of the extrathoracic region in humans = 200 cm<sup>2</sup> (EPA 1994)</p> <p>See Time Adjustment in TRV for calculation of chronic BMCL from intermittent BMCL</p> |
| Duration of exposure                   | 6 hours/day for 5 days/week for 13 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Time Adjustment in TRV?                | $BMCL_{10adj} = BMCL \times 6 \text{ hours} / 24 \text{ hours} \times 5 \text{ days} / 7 \text{ days} = 0.6\text{ppm} \times 6/24 \times 5/7 = 0.011\text{ppm}$                                                                                                                                                                                                                                                                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Oral to inhalation extrapolation       | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Additional notes                       | <p>MRL = <math>BMCL_{HEC} / UF_s</math></p> <p>MRL = <math>0.0027 \text{ ppm} / (3 \times 10) = 0.00009 \text{ ppm} (9 \times 10^{-5} \text{ ppm})</math></p>                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Links to TRV Sources                   | <a href="https://www.atsdr.cdc.gov/toxprofiles/tp67.pdf">https://www.atsdr.cdc.gov/toxprofiles/tp67.pdf</a>                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

#### 4.1.7. EPA ORD PPRTV

TABLE 10. EPA PPRTV FOR 1-METHYLNAPHTHALENE (CAS 91-57-6)

| Variable                | Value                                                              | Comment                                         |
|-------------------------|--------------------------------------------------------------------|-------------------------------------------------|
| PPRTV sub-chronic p-RfC | $3 \times 10^{-5} \text{ mg/m}^3 (0.03 \text{ } \mu\text{g/m}^3)$  | Provisional sub-chronic reference concentration |
| PPRTV chronic p-RfC     | $3 \times 10^{-6} \text{ mg/m}^3 (0.003 \text{ } \mu\text{g/m}^3)$ | Provisional chronic reference concentration     |
| Date                    | March 2024                                                         | --                                              |

|                                                                                                                |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Inhalation toxicity study                                                                                                                                                    | --                                                                                                                                                                                                                                                                                                                                                                |
| Critical study                                                                                                 | Kim, YS; Lee, MJ; Seo, DS; Kim, TH; Kim, MH; Lim, CH. (2020). Thirteen-week inhalation toxicity study of 1-methylnaphthalene in F344 rats. Toxicological Research 36: 13-20. | Same study as ATSDR MRLs<br><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6990237/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6990237/</a>                                                                                                                                                                                                             |
| Species                                                                                                        | Rat                                                                                                                                                                          | --                                                                                                                                                                                                                                                                                                                                                                |
| Target Organ / Effect                                                                                          | Respiratory tract                                                                                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                |
| Description of TRV endpoints/basis for points of departure (POD)                                               | Nasal mucous cell hyperplasia                                                                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                |
| Other Endpoints                                                                                                | Transitional epithelial cell hyperplasia in nasopharyngeal tissues                                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                |
| Uncertainty Factors                                                                                            | <b>Sub-chronic:</b> $3 \times 10 \times 10 = 300$<br><b>Chronic:</b> $3 \times 10 \times 10 \times 10 = 3,000$                                                               | <b>Sub-chronic and Chronic:</b><br>interspecies uncertainty factor [UFA] of 3,<br>a database uncertainty factor [UFD] of 10, and<br>an intraspecies uncertainty factor [UFH] of 10<br><br><b>Chronic only:</b><br>subchronic to chronic uncertainty factor [UFS] of 10                                                                                            |
| POD Method                                                                                                     | BMCL <sub>10</sub> (HEC <sub>ET</sub> )                                                                                                                                      | BMC <sub>10</sub> (HEC <sub>ET</sub> ) = 0.018 mg/m <sup>3</sup><br>BMCL <sub>10</sub> (HEC <sub>ET</sub> ) = 0.009 mg/m <sup>3</sup><br><br>BMC <sub>10</sub> = 10% benchmark concentration;<br>BMCL <sub>10</sub> = The 10% benchmark concentration lower confidence limit<br>HEC <sub>ET</sub> = human equivalent concentration based on extrathoracic effects |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | <p>HEC<sub>ET</sub> of 0.009 mg/m<sup>3</sup></p> <p>“HEC<sub>ET</sub> values are calculated by treating 1-methylnaphthalene as a Category 1 gas and using the following equation from U.S. EPA (1994): HEC = exposure level (mg/m<sup>3</sup>) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × RGDR”</p> <p>RGDR = regional gas dose ratio (animal:human);</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <p>LOAEL = 3.0 mg/m<sup>3</sup></p> <p>RGDR<sub>ET</sub> values of 0.184, 0.183, and 0.182 for males and 0.121, 0.120, and 0.117 for females in the low-, mid-, and high-dose groups, respectively, were calculated as per U.S. EPA (1994) using default values for human VE and human and animal respiratory tissue surface area and animal VE values calculated using study-specific TWA body-weight values of 0.268, 0.266, and 0.265 kg for low-, mid-, and highdose males, respectively, and 0.161, 0.160, and 0.154 kg for low, mid-, and high-dose females, respectively, determined for this review.</p> |
| Duration of exposure                   | 6 hours/day, 5 days/week for 13 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Time Adjustment in TRV?                | Imeddedin HEC <sub>ET</sub> formula above.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Subchronic to chronic UF also applied.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Oral to inhalation extrapolation       | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Additional notes                       | <p>“No chronic inhalation studies were identified for 1-methylnaphthalene. In the absence of available chronic inhalation studies, the POD from the subchronic study by Kim et al. (2020) was selected as a suitable basis for the chronic p-RfC.”</p> <p><b>Subchronic p-RfC =</b><br/>           POD (HEC<sub>ET</sub>) ÷ UFC =<br/>           0.009 mg/m<sup>3</sup> ÷ 300 =<br/>           3 × 10<sup>-5</sup> mg/m<sup>3</sup> (0.03 µg/m<sup>3</sup>)<br/>           “Confidence in the subchronic p-RfC for 1-methylnaphthalene is low”</p> <p><b>Chronic p-RfC =</b><br/>           POD (HEC<sub>ET</sub>) ÷ UFC =<br/>           0.009 mg/m<sup>3</sup> ÷ 3,000 =<br/>           3 × 10<sup>-6</sup> mg/m<sup>3</sup> (0.003 µg/m<sup>3</sup>)<br/>           “Confidence in the chronic p-RfC for 1-methylnaphthalene is low”</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Links to TRV Sources                   | <a href="https://hhpprtv.ornl.gov/issue_papers/Methylnaphthalene1.pdf">https://hhpprtv.ornl.gov/issue_papers/Methylnaphthalene1.pdf</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

## 4.2. 2-methylnaphthalene (CAS 91-57-6)

ERG identified non-carcinogenic health-based screening values for 2-methylnaphthalene. The identified values come from six different state agencies and ATSDR and range from 9.7 to 200 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental or reproductive effects were not identified in any of the reviewed state TRV documentation nor in ATSDR's Toxicological Profile.

2-methylnaphthalene is not present on the DOT list of inhalation hazards.

**TABLE 11. INHALATION TRVs FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)**

| State/Agency      | TRV                     | TRV                     | Classification           | DEQ Notes                                             |
|-------------------|-------------------------|-------------------------|--------------------------|-------------------------------------------------------|
| Maryland DE       | 8-hour* Screening Level | 2.91 µg/m <sup>3</sup>  | Non-cancer, chronic      | Derived from occupational                             |
| Massachusetts DEP | 24-hr TEL               | 14.25 µg/m <sup>3</sup> | Non-cancer, acute        | Derived from occupational                             |
|                   | Annual AAL              | 14.25 µg/m <sup>3</sup> | Non-cancer, chronic      | Derived from occupational                             |
| Michigan EGL      | Annual ITSL             | 10 µg/m <sup>3</sup>    | Non-cancer, chronic      | Derived from LC50                                     |
| New Hampshire DES | 24-hr AAL               | 15 µg/m <sup>3</sup>    | Non-cancer, acute        | Derived from occupational                             |
|                   | Annual AAL              | 9.7 µg/m <sup>3</sup>   | Non-cancer, chronic      | Derived from occupational                             |
| New York DEC      | Annual AGC              | 7.1 µg/m <sup>3</sup>   | Non-cancer, chronic      | Derived from occupational                             |
| Texas TCEQ        | Short-term ESL          | 200 µg/m <sup>3</sup>   | Non-cancer, acute        | Derived from occupational                             |
|                   | Long-term ESL           | 20 µg/m <sup>3</sup>    | Non-cancer, chronic      | Derived from occupational                             |
| ATSDR             | MRL                     | 2 µg/m <sup>3</sup>     | Non-cancer, intermediate | Modified to remove days/week adjustment for acute TRV |

\*Calculated from an occupational exposure limit that assumes an 8-hour workday and a 40-hour workweek

### 4.2.1. Maryland DE

**TABLE 12. MARYLAND DE 8-HOUR SCREENING LEVEL FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)**

| Variable               | Value                  | Comment                                                                                                                         |
|------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 8-hour Screening Level | 2.91 µg/m <sup>3</sup> | Non-carcinogenic, 8-hour screening level. Calculated from a TLV-TWA, "for a conventional 8-hour workday and a 40-hour workweek" |



|                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                          |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Date                                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | Calculated from an ACGIH TLV but year/date not provided. |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit                                                                                                                                                                                                                                                                                                                                                                                                                | Calculated from an ACGIH TLV.                            |
| Critical study                                                                                                 | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Species                                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Target Organ                                                                                                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Uncertainty Factors                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| POD Method                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Human Equivalent Concentration in TRV?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Duration of exposure                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Time Adjustment in TRV?                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Developmental or Reproductive Effects?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Oral to inhalation extrapolation?                                                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation.                            |
| Additional notes                                                                                               | <p>ERG reached out to Maryland DE to obtain the Agency's current TRV values and their derivations. MDE responded by noting that the TRV was set by the ACGIH TLV. Other information was not provided.</p> <p>According to regulation: "If a toxic air pollutant (TAP) has a threshold limit value-time weighted average (TLV-TWA), divide the TLV-TWA by 100 to calculate an 8-hour time-weighted average screening level".</p>            |                                                          |
| Links to TRV Sources                                                                                           | <p><a href="https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx">https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx</a></p> <p><a href="https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03">https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03</a></p> <p>(see email from MDE).</p> |                                                          |

#### 4.2.2. Massachusetts DEP

TABLE 13. MASSACHUSETTS DEP TEL/AAL FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)

| Variable    | Value                   | Comment                           |
|-------------|-------------------------|-----------------------------------|
| TEL and AAL | 14.25 µg/m <sup>3</sup> | Set to same value as naphthalene. |

|                                                                                                                |                                                       |                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date                                                                                                           | February 1990                                         | --                                                                                                                                                                |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit modified by other factors | Regulatory approach calls for identifying a "Most Appropriate Occupational Exposure Limit (MAOL)" and modifying the value based on other available toxicity data. |
| Critical study                                                                                                 | ACGIH                                                 | The source of MAOL is an ACGIH citation from 1987 for Naphthalene.                                                                                                |
| Species                                                                                                        | --                                                    | No information ACGIH 1987 derivation.                                                                                                                             |
| Target Organ                                                                                                   | --                                                    | No information ACGIH 1987 derivation.                                                                                                                             |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                    | No information ACGIH 1987 derivation.                                                                                                                             |
| Other Endpoints                                                                                                | --                                                    | Severity factor = Moderate to severe irritant effects                                                                                                             |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Uncertainty Factors                    | <p>Yes, multiple ‘adjustment factors’</p> <p>Occupational Exposure &gt; Environmental Exposure = 4.2<br/>Derived by converting a 40-hr. workweek occupational exposure to a 168-hr. week continuous environmental exposure (168 hr./40 hr. = 4.2).</p> <p>Adult &gt; Child 1.75 Derived by converting an exposure based on the adult average body weight (70 kg.) and ventilation volume (20 m<sup>3</sup> /24 hrs.) to an exposure based on the child average body weight (20 kg.) and ventilation volume (10 m<sup>3</sup> /24 hrs.) (10 m<sup>3</sup> /24 hrs.) (70 kg.) (20 m<sup>3</sup> /24 hrs.) (20 kg.) = 1.75</p> <p>Occupational Population &gt; High Risk Group (intraspecies variability) 10<br/>Uncertainty factor to extrapolate from an occupational population to high risk groups in the general population.</p> <p>Tox factor 1-10 Uncertainty factor to compensate for inadequacies or limitations in the toxicity data used to set MAOL. 10 is used here.</p> <p>A relative source contribution factor of 20% is also included to account for exposures to given contaminants from sources other than air.<br/>Multiply by 0.2 produces the TEL (Threshold Effects Exposure Limit.)</p> | <p>MAOL divided by adjustment factors = “Adjusted MAOL”.</p> <p>Based on the amount, type, and quality of the data available (and SAR analysis), uncertainty factors called Nonthreshold Effects Uncertainty Factors (NTEUF) are applied to the adjusted MAOL to arrive at an acceptable nonthreshold effects exposure limit (NTEL).</p> <p>Further adjusted to produce a Threshold Effects Exposure Limit.</p> |
| POD Method                             | OEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | MAOL = 10 mg/m <sup>3</sup> for Naphthalene                                                                                                                                                                                                                                                                                                                                                                     |
| Human Equivalent Concentration in TRV? | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | No information available from ACGIH 1987 derivation.                                                                                                                                                                                                                                                                                                                                                            |
| Duration of exposure                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | No information available from ACGIH 1987 derivation.                                                                                                                                                                                                                                                                                                                                                            |
| Time Adjustment in TRV?                | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | OEL occupational exposure adjusted to continuous exposure (see UF above).                                                                                                                                                                                                                                                                                                                                       |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                              |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Considered but none identified.              |
| Oral to inhalation extrapolation       | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Not explicit in calculation of TRV from OEL. |
| Additional notes                       | <p>Calculation of AAL shown below:</p> $\text{Adjusted MAOL} = \text{MAOL} / (4.2 * 1.75 * 10)$ $= 52.37 \text{ mg/m}^3 / (4.2 * 71)$ $= 71.25 \text{ } \mu\text{g/m}^3 \text{ (13.61 ppb)}$ <p>Where: 4.2 = Continuous time adjustment<br/>And 1.75 = Adult to child adjustment</p> $\text{TEL} = \text{Adjusted MAOL} * 0.2$ $= 71.25 \text{ } \mu\text{g/m}^3 * 0.2$ $= 14.25 \text{ } \mu\text{g/m}^3 \text{ (13.61 ppb)}$ <p>AAL = TEL since there are no carcinogenic concerns.</p> <p>MAOL = 52.37 mg/m<sup>3</sup> (10ppm)</p> <p>Appears to be set based on ACGIH values for Naphthalene.</p>                                                                                                     |                                              |
| Links to TRV Sources                   | <p><a href="https://www.mass.gov/doc/the-chemical-health-effects-assessment-methodology-the-method-to-derive-allowable-ambient-0">https://www.mass.gov/doc/the-chemical-health-effects-assessment-methodology-the-method-to-derive-allowable-ambient-0</a></p> <p><a href="https://www.mass.gov/doc/methodology-for-updating-guidelines-allowable-ambient-limits-threshold-effect-exposure/download">https://www.mass.gov/doc/methodology-for-updating-guidelines-allowable-ambient-limits-threshold-effect-exposure/download</a></p> <p><a href="https://www.mass.gov/info-details/massdep-ambient-air-toxics-guidelines">https://www.mass.gov/info-details/massdep-ambient-air-toxics-guidelines</a></p> |                                              |

#### 4.2.3. Michigan EGLE

TABLE 14. MICHIGAN EGLE ITSL FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)

| Variable                                                                                                       | Value                                                    | Comment                                  |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------|
| ITSL                                                                                                           | 10 $\mu\text{g/m}^3$                                     | Non-carcinogenic, annual screening level |
| Date                                                                                                           | December 30, 2002                                        | --                                       |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Derived from a short-term (4-hour) inhalation rat study. | --                                       |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                   |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Critical study                                                    | Korsak et al., 1998. Toxic effects of acute inhalation exposure to 1-MN and 2-MN in experimental animals. Int J Occup Med Environ Health 11: 335-342.                                                                                                                                                                                                                                                                                                                                                                                                                                                | <a href="https://pubmed.ncbi.nlm.nih.gov/10028200/">https://pubmed.ncbi.nlm.nih.gov/10028200/</a> |
| Species                                                           | Rat                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | --                                                                                                |
| Target Organ                                                      | Death (LC50)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | --                                                                                                |
| Description of TRV endpoints/ basis for points of departure (POD) | Death                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Regulatory LC50 formula used with highest concentration where no deaths were observed.            |
| Other Endpoints                                                   | Rotarod performance, paw sensitivity to heat (a measure of analgesia) and changes in respiration rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | --                                                                                                |
| Uncertainty Factors                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | See note below                                                                                    |
| POD Method                                                        | LC50 (highest concentration where no deaths occurred)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | No deaths occurred at the highest concentration, which was used in an LC50 formula.               |
| Human Equivalent Concentration in TRV?                            | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | --                                                                                                |
| Duration of exposure                                              | 4 hours                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                |
| Time Adjustment in TRV?                                           | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | --                                                                                                |
| Developmental or Reproductive Effects?                            | No direct mention of developmental or reproductive effects in TRV document.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 20% growth retardation noted at high doses by Murata et al., 1993                                 |
| Oral to inhalation extrapolation                                  | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                   |
| Additional notes                                                  | <p>ITSL calculated based on approach in <a href="#">R232(1)(f)</a>:<br/> <math>ITSL = 527 \text{ mg/m}^3 / (500 * 100) = 10 \text{ } \mu\text{g/m}^3</math> with annual averaging. Highest concentration, which had no deaths was used in place of LC50. Note: it is not clear what uncertainty factors the 500 and 100 represent but this is the formula written into regulation when using LC50.</p> <p>24-hour ITSL was also calculated based on Murata et al., 1993 (used for 1-methylnaphthalene), but was deemed inappropriate given it would exceed the 24-hour particulate matter NAAQS.</p> |                                                                                                   |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://www.michigan.gov/egle/-/media/Project/Websites/egle/Documents/Programs/AQD/toxics/screening-levels-alphabetical.pdf">https://www.michigan.gov/egle/-/media/Project/Websites/egle/Documents/Programs/AQD/toxics/screening-levels-alphabetical.pdf</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/91-57-6/91-57-6_annual_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/91-57-6/91-57-6_annual_ITSL.pdf</a><br><br><a href="https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level">https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level</a> |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.2.4. New Hampshire DES

TABLE 15. NEW HAMPSHIRE DES 24-HOUR AND ANNUAL AAL FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)

| Variable                                                                                                       | Value                                                                                                                                                                | Comment                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24-Hour AAL                                                                                                    | 15 µg/m <sup>3</sup>                                                                                                                                                 | 24-hour ambient air limit                                                                                                                                                                                                                                                                                                       |
| Annual AAL                                                                                                     | 9.7 µg/m <sup>3</sup>                                                                                                                                                | Annual ambient air limit                                                                                                                                                                                                                                                                                                        |
| Date                                                                                                           | 1996                                                                                                                                                                 | --                                                                                                                                                                                                                                                                                                                              |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit modified with toxicity data from an oral toxicity study                                                                                  | Regulatory approach calls for setting the AAL based on modifying the ACGIH value based on other available toxicity data. See additional notes below.                                                                                                                                                                            |
| Critical study                                                                                                 | 1) ACGIH OEL,<br>2) Dangerous Properties of Industrial Materials, N. Irving Sax, page 2268 (1996), cited in the Hazardous Substances Data Bank (HSDB)<br>3) EPA IRIS | Regulatory approach calls for setting the AAL based on modifying the ACGIH value based on other available toxicity data. See additional notes below.<br><br>"The compound has a reference dose (RfD) listed on the USEPA's Integrated Risk Information System (IRIS) with a critical effect of pulmonary alveolar proteinosis." |
| Species                                                                                                        | Rat                                                                                                                                                                  | Rat study was used to determine acute toxicity. IRIS was used for chronic toxicity.                                                                                                                                                                                                                                             |
| Target Organ                                                                                                   | --                                                                                                                                                                   | See comment in 'Description of TRV endpoints'                                                                                                                                                                                                                                                                                   |

|                                                                   |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                           |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Description of TRV endpoints/ basis for points of departure (POD) | --                                                                                                                                                                                                                                                                                                                          | The underlying source for the old ACGIH OEL value used is not available. Death (LD50) was the endpoint in the acute rat study. Pulmonary alveolar proteinosis was the critical effect identified in IRIS. |
| Other Endpoints                                                   | --                                                                                                                                                                                                                                                                                                                          | --                                                                                                                                                                                                        |
| Uncertainty Factors                                               | Annual Combined UF = 71<br>24-hour Combined UF = 198.8 (see formula below)                                                                                                                                                                                                                                                  | New Hampshire assigned 2-methylnaphthalene a Toxicity Factor = II and Time Adjustment Factor = D which correspond to SF = 71 and TAF = 2.8.                                                               |
| POD Method                                                        | OEL                                                                                                                                                                                                                                                                                                                         | OEL = 2900 µg/m <sup>3</sup>                                                                                                                                                                              |
| Human Equivalent Concentration in TRV?                            | --                                                                                                                                                                                                                                                                                                                          | Not explicit in calculation from OEL.                                                                                                                                                                     |
| Duration of exposure                                              | --                                                                                                                                                                                                                                                                                                                          | Varies by study.                                                                                                                                                                                          |
| Time Adjustment in TRV?                                           | Yes<br><br>For the Annual AAL, NHDES adjusted the OEL by a factor of 4.2 = 24 hrs per day / 8 hrs per work day) * (7 days per week / 5 days work week)<br><br>For the 24-hour AAL, NHDES assigned 1-methylnaphthalene a 'Time Adjustment Factor (TAF)' based on regulatory criteria 'D,' which corresponds to a TAF of 2.8. | See formulas in 'additional notes' below.                                                                                                                                                                 |
| Developmental or Reproductive Effects?                            | No                                                                                                                                                                                                                                                                                                                          | No mention of developmental or reproductive effects/studies.                                                                                                                                              |
| Oral to inhalation extrapolation                                  | No                                                                                                                                                                                                                                                                                                                          | Not explicit in calculation of TRV from OEL.                                                                                                                                                              |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | <p>Calculation of AALs is shown below:</p> <p><u>Annual AAL</u></p> $= \text{OEL} / (4.2 * \text{SF})$ $= 2900 \mu\text{g}/\text{m}^3 / (4.2 * 71)$ $= 2900 \mu\text{g}/\text{m}^3 / 298.2$ $= 9.73 \mu\text{g}/\text{m}^3$ <p>Where: 4.2 = (24 hrs per day / 8 hrs per work day) * (7 days per week / 5 days work week).</p> <p><u>24-hour AAL</u></p> $= \text{OEL} / (\text{SF} * \text{TAF})$ $= 2900 \mu\text{g}/\text{m}^3 / (71 * 2.8)$ $= 2900 \mu\text{g}/\text{m}^3 / (198.8)$ $= 14.6 \mu\text{g}/\text{m}^3$ <p>Note the ACGIH OEL of 2,900 <math>\mu\text{g}/\text{m}^3</math> appears outdated as the current ACGIH Threshold Limit Value (TLV) is 0.3 <math>\text{mg}/\text{m}^3</math> (300 <math>\mu\text{g}/\text{m}^3</math>).</p> <p>Same calculation as 1-methylnaphthalene.</p> |
| Links to TRV Sources | <p><a href="https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance">https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance</a></p> <p><a href="https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/env-a-1400.pdf">https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/env-a-1400.pdf</a></p> <p>See email from New Hampshire DES for documentation of derivation.</p>                                                                                                                                                                                                                                                                                                                                                                                |

#### 4.2.5. New York DEC

TABLE 16. NEW YORK DEC AGC FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)

| Variable | Value                        | Comment                                                                                                                            |
|----------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| AGC      | 7.1 $\mu\text{g}/\text{m}^3$ | Annual Guideline Concentration                                                                                                     |
| Date     | February 12, 2021            | Date of Issue for: " <a href="#">Guidelines for the Evaluation and Control of Ambient Air Contaminants Under 6NYCRR Part 212</a> " |



|                                                                                                                |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational exposure limit                                                                                                                                                                       | Based on 2018 ACGIH's TLV-TWAs                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Critical study                                                                                                 | American Conference of Governmental Industrial Hygienists (ACGIH) 2018. Documentation of Threshold Limit Values and Biological Exposure Indices, 7th Edition – 2015 Supplement. Cincinnati, Ohio. | The 2018 ACGIH TLV used by NYDEC appears to be the same as the current TLV (300 µg/m <sup>3</sup> ).                                                                                                                                                                                                                                                                                                                                                             |
| Species                                                                                                        | Rat, Mice                                                                                                                                                                                         | Based on current ACGIH documentation.                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Target Organ                                                                                                   | Respiratory tract, Lung, Liver                                                                                                                                                                    | Based on current ACGIH documentation.                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Upper respiratory tract irritation, lung damage, liver effects                                                                                                                                    | Based on current ACGIH documentation.                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                | Other studies reference skin and eye irritation in ACGIH documentation.                                                                                                                                                                                                                                                                                                                                                                                          |
| Uncertainty Factors                                                                                            | UF of 42 (inferred).                                                                                                                                                                              | <p>The UF is defined in regulation by the 'toxicity level', which can be High, Moderate, or Low. The UF is 420 for Medium or High toxicity substances and 42 for Low toxicity substances. (See additional notes).</p> <p>No toxicity level is explicitly defined by NYDOH for 1-methylnaphthalene; however, based on the current ACGIH value of 300 µg/m<sup>3</sup>, and uncertainty factor of 42 is likely used to derive the AGC of 7.1 µg/m<sup>3</sup>.</p> |
| POD Method                                                                                                     | --                                                                                                                                                                                                | Unclear POD method for ACGIH derivation.                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Human Equivalent Concentration in TRV?                                                                         | Not explicit in NYDE calculation.                                                                                                                                                                 | Unclear on human equivalent concentration used in ACGIH derivation.                                                                                                                                                                                                                                                                                                                                                                                              |
| Duration of exposure                                                                                           | --                                                                                                                                                                                                | Unclear on duration of exposure from ACGIH derivation.                                                                                                                                                                                                                                                                                                                                                                                                           |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                       |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Time Adjustment in TRV?                | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | The uncertainty factors are based on adjusting the 8-hr workday exposure to a 24-hr exposure and a 5-day work week to 7-day exposure. |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | No developmental or reproductive effects listed in current ACGIH documentation.                                                       |
| Oral to inhalation extrapolation       | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | --                                                                                                                                    |
| Additional notes                       | <p>“AGCs are calculated by starting with the TLV for an air contaminant and adjusting it by an uncertainty factor. The uncertainty factor for a chemical classified as HIGH or MODERATE toxicity is 420. The uncertainty factor for a chemical classified as LOW toxicity is 42. The uncertainty factors are based on adjusting the 8-hr work day exposure to a 24-hr exposure and a 5-day work week to 7-day exposure, and by applying an additional factor of 10 for LOW toxicity or 100 for MODERATE and HIGH toxicity contaminants to compensate for applying an occupational standard to the general population.”</p> <p>Same source and values as 1-methylnaphthalene.</p> |                                                                                                                                       |
| Links to TRV Sources                   | <p><a href="https://dec.ny.gov/environmental-protection/air-quality/controlling-pollution-from-facilities/air-toxics-program">https://dec.ny.gov/environmental-protection/air-quality/controlling-pollution-from-facilities/air-toxics-program</a></p> <p><a href="https://dec.ny.gov/docs/air_pdf/dar1.pdf">https://dec.ny.gov/docs/air_pdf/dar1.pdf</a></p>                                                                                                                                                                                                                                                                                                                    |                                                                                                                                       |

#### 4.2.6. Texas TCEQ

TABLE 17. TEXAS TCEQ SHORT- AND LONG-TERM ESL FOR 2- METHYLNAPHTHALENE (CAS 91-57-6)

| Variable                                                                                                       | Value                             | Comment                                                 |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------|
| Short-Term ESL                                                                                                 | 200 µg/m <sup>3</sup>             | Short-Term defined as one hour                          |
| Long-Term ESL                                                                                                  | 20 µg/m <sup>3</sup>              | Long-Term defined as 70 years                           |
| Date                                                                                                           | November 17, 2014                 |                                                         |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit (OEL) | TRV derived from “Russia OEL” of 20 mg/m <sup>3</sup> . |
| Critical study                                                                                                 | Russian OEL                       | Original source of Russia OEL was not available.        |
| Species                                                                                                        | --                                | --                                                      |
| Target Organ                                                                                                   | --                                | --                                                      |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                | --                                                      |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |
|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Other Endpoints                        | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| Uncertainty Factors                    | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| POD Method                             | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| Human Equivalent Concentration in TRV? | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| Duration of exposure                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| Time Adjustment in TRV?                | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -- |
| Oral to inhalation extrapolation       | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |    |
| Additional notes                       | <p>Values are “Interim.” which “indicates that the ESL is current and will be reviewed by the Toxicology Division at a later date. Also, interim ESLs may be updated pending the release of updated toxicity information or odor data.”</p> <p>Same source and values as 2-methylnaphthalene. The TRV documentation has the following note:</p> <p>“ATSDR groups naphthalene and 1- and 2-methylnaphthalene together in it's Tox Profile, no inhalation data is available for 1-methylnaphthalene, but LD50 is much higher than for naphthalene, surrogating would raise ESLs significantly, ACGIH based it's values on an RD50, which does not follow with the TCEQ guidelines, to be conservative, use Russia's OEL to calculate ESLs.”</p> |    |
| Links to TRV Sources                   | <p>TAMIS database -&gt; Start Report -&gt; Tox Document Report -&gt; Next -&gt; Create Report for CAS number 90-12-0:<br/> <a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a> </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                       |    |

#### 4.2.7. ATSDR

TABLE 18. ATSDR MRL FOR 2-METHYLNAPHTHALENE (CAS 91-57-6)

| Variable                                                                                                       | Value                                        | Comment                                                             |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------|---------------------------------------------------------------------|
| MRL                                                                                                            | 2 µg/m <sup>3</sup> (3x10 <sup>-4</sup> ppm) | Provisional Intermediate exposure MRL                               |
| Date                                                                                                           | May 2024                                     | Updated draft Tox Profile released over the course of this project. |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Inhalation toxicity study                    | --                                                                  |

|                                                                  |                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                   | Swiercz R, Wąsowicz W, Stetkiewicz J, Gromadzińska J, Majcherek W. 4-Week inhalation toxicity of 2-methylnaphthalene in experimental animals. Int J Occup Med Environ Health. 2011 Dec;24(4):399-408. doi: 10.2478/s13382-011-0036-9.                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Species                                                          | Rat                                                                                                                                                                                                                                                                                                  | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Target Organ / Effect                                            | Respiratory system                                                                                                                                                                                                                                                                                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Description of TRV endpoints/basis for points of departure (POD) | Bronchial goblet cell metaplasia                                                                                                                                                                                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Other Endpoints                                                  | Serum chemistry changes, reduced relative weight of liver, heart, kidney.                                                                                                                                                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Uncertainty Factors                                              | UF = 3 x 10 x 10 = 300                                                                                                                                                                                                                                                                               | UF (animal to human) = 3<br>UF (sensitive humans) = 10<br>UF (use of LOAEL) = 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| POD Method                                                       | LOAEL <sub>HEC</sub>                                                                                                                                                                                                                                                                                 | LOAEL = 0.34 ppm<br>LOAEL <sub>adj</sub> = 0.061 ppm (time adjustment)<br>LOAEL <sub>HEC</sub> = 0.081 ppm                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Human Equivalent Concentration in TRV?                           | $RGDR_{TB} = \frac{(Dose_{TB})_a}{(Dose_{TB})_h} = \frac{(\frac{V_E}{SA_{TB}})_a}{(\frac{V_E}{SA_{TB}})_h} \frac{(e^{-\frac{SA_{ET}}{V_E}})_a}{(e^{-\frac{SA_{ET}}{V_E}})_h}$ <p>RGDR<sub>TB</sub> = 1.33</p> <p>LOAEL<sub>HEC</sub> = LOAEL<sub>ADJ</sub> x RGDR = 0.061 ppm x 1.33 = 0.081 ppm</p> | <p><b>RGDR<sub>TB</sub></b> = Rat-specific regional gas dose ratio that corresponds with the tracheobronchial effect</p> <p><b>ET</b> = Extrathoracic</p> <p><b>TB</b> = Tracheobronchial</p> <p><b>[V<sub>E</sub>]<sub>a</sub></b> = minute volume for rats = 0.141 L/min</p> <p><b>SA<sub>TB a</sub></b> = TB surface area for rats = 22.5 cm<sup>2</sup></p> <p><b>e<sup>-(SA<sub>ET</sub>/V<sub>E</sub>)<sub>a</sub></sup></b> = Fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in rats = 0.899</p> <p><b>[V<sub>E</sub>]<sub>h</sub></b> = minute volume for humans = 13.8 L/min</p> <p><b>SA<sub>TB h</sub></b> = TB surface area for humans = 3200 cm<sup>2</sup></p> <p><b>e<sup>-(SA<sub>ET</sub>/V<sub>E</sub>)<sub>h</sub></sup></b> = Fraction of chemical concentration penetrating the ET region and available for uptake in the TB region in humans = 0.986</p> |
| Duration of exposure                                             | 6 hours/day, 5 days/week for 4 weeks                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|                                        |                                                                                                             |                                 |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------|
| Time Adjustment in TRV?                | LOAELadj = LOAEL * 6hr/24hr * 5day/7days = 0.061ppm                                                         | --                              |
| Developmental or Reproductive Effects? | No                                                                                                          | Considered but none identified. |
| Oral to inhalation extrapolation       | No                                                                                                          |                                 |
| Additional notes                       | MRL = LOAEL <sub>HEC</sub> / UFs = 0.081 ppm / (3x10x10) ≈ 0.0003 ppm (0.002 mg/m <sup>3</sup> )            |                                 |
| Links to TRV Sources                   | <a href="https://www.atsdr.cdc.gov/toxprofiles/tp67.pdf">https://www.atsdr.cdc.gov/toxprofiles/tp67.pdf</a> |                                 |

### 4.3. Copper naphthenate (CAS 1338-02-9)

ERG identified non-carcinogenic health-based screening values for copper naphthenate. The identified values come from two different state agencies and ECHA. Values from Maryland DE and ECHA range from 26.558 µg/m<sup>3</sup> to 1,940 µg/m<sup>3</sup>. TCEQ uses particulate matter national ambient air quality standards (NAAQS) as a surrogate for its TRVs for copper naphthenate. Cancer screening values were not identified.

Developmental and reproductive effects were not identified for copper naphthenate.

Copper naphthenate is not present on the DOT list of inhalation hazards.

**TABLE 19. INHALATION TRVs FOR COPPER NAPHTHENATE (CAS 1338-02-9)**

| State/Agency | TRV                         | TRV                                               | Classification      | DEQ Notes                                                                                       |
|--------------|-----------------------------|---------------------------------------------------|---------------------|-------------------------------------------------------------------------------------------------|
| Maryland DE  | 8-hour* Screening Level     | 26.558 µg/m <sup>3</sup>                          | Non-cancer, chronic | Derived from occupational                                                                       |
| Texas TCEQ   | Short-Term ESL              | Must meet NAAQs**                                 | Non-cancer, acute   | No values listed but they apply their toxicity information for copper and compounds to this TAC |
|              | Long-Term ESL               | Must meet NAAQs**                                 | Non-cancer, chronic | No values listed but they apply their toxicity information for copper and compounds to this TAC |
| ECHA         | Occupational Long-Term DNEL | 1,940 µg/m <sup>3</sup> (1.94 mg/m <sup>3</sup> ) | Non-cancer, chronic | Based on copper toxicity – not copper                                                           |

|  |                                   |                                                 |                     |                                       |
|--|-----------------------------------|-------------------------------------------------|---------------------|---------------------------------------|
|  |                                   |                                                 |                     | naphthenate specifically              |
|  | General Population Long-Term DNEL | 380 µg/m <sup>3</sup> (0.38 mg/m <sup>3</sup> ) | Non-cancer, chronic | Based on copper toxicity – not copper |

\*\* Calculated from an occupational exposure limit that assumes an 8-hour workday and a 40-hour workweek

\*See Texas subsection

DEQ does not propose to use any of the values listed in the table above, but DEQ does propose to apply the TRV for copper and copper compounds to this TAC (i.e. use copper and compounds as a surrogate for copper naphthenate) like TCEQ and ECHA did.

#### 4.3.1. Maryland DE

TABLE 20. MARYLAND DE 8-HOUR SCREENING LEVEL FOR COPPER NAPHTHENATE (CAS 1338-02-9)

| Variable                                                                                                       | Value                       | Comment                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 8-hour Screening Level                                                                                         | 26.558 µg/m <sup>3</sup>    | Non-carcinogenic, 8-hour screening level. Calculated from a TLV-TWA, “for a conventional 8-hour workday and a 40-hour workweek” |
| Date                                                                                                           | --                          | Calculated from an ACGIH TLV but year/date not provided.                                                                        |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit | Calculated from an ACGIH TLV.                                                                                                   |
| Critical study                                                                                                 | --                          | No information on derivation.                                                                                                   |
| Species                                                                                                        | --                          | No information on derivation.                                                                                                   |
| Target Organ                                                                                                   | --                          | No information on derivation.                                                                                                   |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                          | No information on derivation.                                                                                                   |
| Other Endpoints                                                                                                | --                          | No information on derivation.                                                                                                   |
| Uncertainty Factors                                                                                            | --                          | No information on derivation.                                                                                                   |
| POD Method                                                                                                     | --                          | No information on derivation.                                                                                                   |
| Human Equivalent Concentration in TRV?                                                                         | --                          | No information on derivation.                                                                                                   |
| Duration of exposure                                                                                           | --                          | No information on derivation.                                                                                                   |
| Time Adjustment in TRV?                                                                                        | --                          | No information on derivation.                                                                                                   |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                            |                               |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Developmental or Reproductive Effects? | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation. |
| Oral to inhalation extrapolation?      | --                                                                                                                                                                                                                                                                                                                                                                                                                                         | No information on derivation. |
| Additional notes                       | <p>ERG reached out to Maryland DE to obtain the Agency's current TRV values and their derivations. MDE responded by noting that the TRV was set by the ACGIH TLV. Other information was not provided.</p> <p>According to regulation: "If a toxic air pollutant (TAP) has a threshold limit value-time weighted average (TLV-TWA), divide the TLV-TWA by 100 to calculate an 8-hour time-weighted average screening level".</p>            |                               |
| Links to TRV Sources                   | <p><a href="https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx">https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx</a></p> <p><a href="https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03">https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03</a></p> <p>(see email from MDE).</p> |                               |

#### 4.3.2. Texas TCEQ

On September 4, 2015, TCEQ assigned the National Ambient Air Quality Standards for particulate matter as a "surrogate" for copper naphthenate's short-term and long-term ESL. ERG emailed TCEQ to request additional information, but TCEQ was unable to provide additional information on this derivation.

A list of the TCEQ ESLs with this information can be found as a download here:

<https://www.tceq.texas.gov/toxicology/esl/ESLMain.html>

#### 4.3.3. ECHA

**TABLE 21. ECHA OCCUPATIONAL AND GENERAL POPULATION DNELS FOR COPPER NAPHTHENATE (CAS 1338-02-9)**

| Variable                                                                                                       | Value                                                  | Comment                 |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------|
| Occupational Long-term DNEL                                                                                    | 1,940 µg/m <sup>3</sup> (1.94 mg/m <sup>3</sup> )      | Derived No Effect Level |
| General Population Long-term DNEL                                                                              | 380 µg/m <sup>3</sup> (0.38 mg/m <sup>3</sup> )        | Derived No Effect Level |
| Date                                                                                                           | December 12, 2023                                      | --                      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Subacute inhalation toxicity study of CuO <sub>2</sub> | --                      |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                         |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Critical study                                                    | Kirkpatrick D. 2010. A four-week inhalation toxicity study of cuprous oxide in Sprague-Dawley rats with a time course evaluation and a 13-week recovery evaluation. WIL Research Labs, LLC. WIL-708003.                                                                                                                                                                                                                                                                                                                                                                                                                | --                                                                      |
| Species                                                           | Rat                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | --                                                                      |
| Target Organ                                                      | Lungs / Immune System                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | --                                                                      |
| Description of TRV endpoints/ basis for points of departure (POD) | CuO <sub>2</sub> : Macrophages in the lungs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                                      |
| Other Endpoints                                                   | CuO <sub>2</sub> : increase in neutrophils, lactate dehydrogenase and protein in bronchoalveolar lavage fluid; lung inflammation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | --                                                                      |
| Assessment Factors                                                | Yes but unclear which factors were applied for derivation of DNEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | --                                                                      |
| POD Method                                                        | NOAEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | LOEL = 0.2 mg/m <sup>3</sup> air<br>NOAEL = ≥ 2.0 mg/m <sup>3</sup> air |
| Human Equivalent Concentration in TRV?                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Possibly through UF but unclear from documentation                      |
| Duration of exposure                                              | 6 hours per day for 28 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                                      |
| Time Adjustment in TRV?                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Possibly through UF but unclear from documentation                      |
| Developmental or Reproductive Effects?                            | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                         |
| Oral to inhalation extrapolation                                  | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                         |
| Additional notes                                                  | Documentation and derivation are not clear.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                         |
| Links to TRV Sources                                              | <a href="https://chem.echa.europa.eu/100.014.234/dossier-view/34645ba5-9f80-4c4d-ab7f-e91be436bfab/ee5b248e-e326-4c2e-8927-e4047c2a135a_b8679f61-6287-414e-8c3e-6b6b01ba21aa">https://chem.echa.europa.eu/100.014.234/dossier-view/34645ba5-9f80-4c4d-ab7f-e91be436bfab/ee5b248e-e326-4c2e-8927-e4047c2a135a_b8679f61-6287-414e-8c3e-6b6b01ba21aa</a><br><br><a href="https://echa.europa.eu/documents/10162/13632/information_requirement_s_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258">https://echa.europa.eu/documents/10162/13632/information_requirement_s_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258</a> |                                                                         |

4.4. 4,5-Dichloro-2-octyl-3(2H)-isothiazolone (DCOI) (CAS 64359-81-5)  
ERG identified non-carcinogenic health-based screening values for 4,5-Dichloro-2-octyl-3(2H)-isothiazolone (DCOI). The identified values come from Texas and the EPA Office of Pesticide Programs, and values range from 0.06 to 0.6 µg/m<sup>3</sup> (ESLs) and 0.002 to 0.03 mg/kg/day (RfDs). Note that the OPP



RfDs are oral RfDs, which were not extrapolated to inhalation values but are summarized here per request by Oregon DOH. Cancer screening values were not identified.

Developmental toxicity endpoints were observed in the EPA OPP documentation.

DCOI is not present on the DOT list of inhalation hazards.

**TABLE 22. INHALATION TRVs FOR 4,5-DICHLORO-2-OCTYL-3(2H)-ISOTHIAZOLONE (DCOI) (CAS 64359-81-5)**

| State/Agency | TRV            | TRV                    | Classification      | DEQ Notes                                    |
|--------------|----------------|------------------------|---------------------|----------------------------------------------|
| Texas TCEQ   | Short-term ESL | 0.6 µg/m <sup>3</sup>  | Non-cancer, acute   | No publicly available derivation information |
|              | Long-term ESL  | 0.06 µg/m <sup>3</sup> | Non-cancer, chronic | No publicly available derivation information |
| EPA OPP      | Acute RfD      | 0.03 mg/kg/day         | Non-cancer, acute   | Oral value only                              |
|              | Chronic RfD    | 0.002 mg/kg/day        | Non-cancer, chronic | Oral value only                              |

DEQ does not propose any inhalation TRV for this TAC. Values in table above are not defensible by DEQ.

#### 4.4.1. Texas TCEQ

On November 3, 1997, TCEQ assigned the short-term ESL to DCOI of 0.6 µg/m<sup>3</sup> and a long-term ESL of 0.06 µg/m<sup>3</sup>. ERG emailed TCEQ to request additional information but TCEQ was unable to provide additional information on this derivation.

A list of the TCEQ ESLs with this information can be found as a download here:

<https://www.tceq.texas.gov/toxicology/esl/ESLMain.html>

#### 4.4.2. EPA OPP

**TABLE 23. EPA OPP ACUTE AND CHRONIC RfD FOR DCOI (CAS 64359-81-5)**

| Variable                                                                                                       | Value                                                                                      | Comment  |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------|
| Acute (One-Day) RfD                                                                                            | 0.03 mg/kg/day                                                                             | Oral RfD |
| Chronic (Lifetime) RfD                                                                                         | 0.002 mg/kg/day                                                                            | Oral RfD |
| Date                                                                                                           | December 8, 1999                                                                           | --       |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | <b>Acute:</b> developmental oral toxicity study<br><br><b>Chronic:</b> oral toxicity study | --       |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                   |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | <b>Acute:</b> MRID Number 43471604<br><b>Chronic:</b> MRID Number 42214903                                                                                                                                                                                                                                                                                      | Only executive summaries provided for studies.                                                                                                    |
| Species                                                           | Rat                                                                                                                                                                                                                                                                                                                                                             | -                                                                                                                                                 |
| Target Organ                                                      | <b>Acute:</b> Skeletal system (developmental)<br><b>Chronic:</b> Hematological changes                                                                                                                                                                                                                                                                          | -                                                                                                                                                 |
| Description of TRV endpoints/ basis for points of departure (POD) | <b>Acute:</b> Increased incidence and severity of wavy ribs in offspring<br><b>Chronic:</b> decreased mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)                                                                                                                                    | -                                                                                                                                                 |
| Other Endpoints                                                   | <b>Acute:</b> Reduced food consumption and decreased body weight gain in dams<br><b>Chronic:</b> Hyperplasia of the mucosa and granulation of the tunica propria mucosa of the non-glandular stomach. Also, in the highest dose group, clinical signs of toxicity (anal staining, reduced spontaneous movements, salivation, hypothermia, abdominal distension) | --                                                                                                                                                |
| Uncertainty Factors                                               | <b>Acute:</b> $UF_{total} = 10 \times 10 = 100$<br><b>Chronic:</b> $UF_{total} = 10 \times 10 \times 10 = 1000$                                                                                                                                                                                                                                                 | <b>Acute and chronic:</b><br>UF (animal to human) = 10<br>UF (sensitive individuals) = 10<br><b>Chronic:</b><br>UF (lack of chronic studies) = 10 |
| POD Method                                                        | <b>Acute:</b> LOAEL<br><b>Chronic:</b> NOAEL                                                                                                                                                                                                                                                                                                                    | <b>Acute</b> NOAEL = 30 mg/kg/day<br><b>Acute</b> LOAEL = 100 mg/kg/day<br><b>Chronic</b> NOAEL = 20 mg/kg/day                                    |
| Human Equivalent Concentration in TRV?                            | No                                                                                                                                                                                                                                                                                                                                                              | Not explicit in RfD calculation.                                                                                                                  |
| Duration of exposure                                              | <b>Acute:</b> 7 days (GD 6-15)<br><b>Chronic:</b> 28 days                                                                                                                                                                                                                                                                                                       | <b>Chronic:</b> Similar lesion in the stomach were observed in a 90-day study but at a lower dose in the 28-day study.                            |
| Time Adjustment in TRV?                                           | Not explicit in calculations.                                                                                                                                                                                                                                                                                                                                   | Chronic has an UF related to use of sub-chronic study.                                                                                            |
| Developmental or Reproductive Effects?                            | Developmental                                                                                                                                                                                                                                                                                                                                                   | From acute dietary study: "Increased number of litters with wavy ribs".                                                                           |

|                                  |                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral to inhalation extrapolation | No                                                                                                                                                                                                                                                                                                                                         |
| Additional notes                 | <p>Acute RfD = LOAEL/UF<sub>total</sub> = 30 mg/kg / 100 = 0.3 mg/kg</p> <p>Chronic RfD = LOAEL/UF<sub>total</sub> = 20 mg/kg / 1000 = 0.002 mg/kg</p> <p>The report also provides some information on an inhalation study which has a NOAEL of 0.02 mg/m<sup>3</sup> (0.0037 mg/kg/day), but doesn't expand on this or derive an RfC.</p> |
| Links to TRV Sources             | <a href="https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/128101/128101-034.pdf">https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/128101/128101-034.pdf</a>                                                                                                                                  |

#### 4.5. Perfluorobutanoic acid (PFBA) (CAS 375-22-4)

ERG identified non-carcinogenic health-based screening values for PFBA. The identified values come from Minnesota and Texas and range from 3.5 to 10 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental or reproductive effects were cited for PFBA in both Minnesota and Texas TRV documentation. In addition, [ATSDR's 2022 Toxicological Profile](#) noted one study that observed delayed developmental milestones in rats (Das et al. 2008).

PFBA is not present on the DOT list of inhalation hazards.

**TABLE 24. INHALATION TRVs FOR PERFLUOROBUTANOIC ACID (PFBA) (CAS 375-22-4)**

| State/Agency | TRV Type        | TRV Value             | Classification          | DEQ Notes                                                                             |
|--------------|-----------------|-----------------------|-------------------------|---------------------------------------------------------------------------------------|
| Minnesota DH | Short-term RAA  | 10 µg/m <sup>3</sup>  | Non-cancer, acute       | Unmodified                                                                            |
|              | Sub-chronic RAA | 10 µg/m <sup>3</sup>  | Non-cancer, sub-chronic | Not needed because same value as acute                                                |
|              | Chronic RAA     | 10 µg/m <sup>3</sup>  | Non-cancer, chronic     | Not needed because same value as acute                                                |
| Texas TCEQ   | RfC             | 3.5 µg/m <sup>3</sup> | Non-cancer, chronic     | Unmodified – derived from newer oral tox study (2022) than Minnesota DH chronic value |

### 4.5.1. Minnesota DH

TABLE 25. MINNESOTA DH RAA FOR PFBA (CAS 375-22-4)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                                                                                        | Comment                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Short-term Non-Cancer RAA                                                                                      | 10 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                         | Short-term (>24 hours; < 30 days); though short-term has a different derivation than sub-chronic and chronic.              |
| Sub-chronic Non-Cancer RAA                                                                                     | 10 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                         | Sub-chronic (>30 days and <10% of lifetime) sub-chronic and chronic have same derivation.                                  |
| Chronic Non-Cancer RAA                                                                                         | 10 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                         | Chronic (>10% of lifetime) all have the same value of 10 µg/m <sup>3</sup> , sub-chronic and chronic have same derivation. |
| Date                                                                                                           | September 2021                                                                                                                                                                                                                                                                                                                                                                                                                               | --                                                                                                                         |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                                                                                                                                                                                                                                                                                                                                                                                                                               | All three are based on RfDs from oral rat studies.                                                                         |
| Critical study                                                                                                 | <p><b>Short-term:</b> NOTOX 2007a. Project 470677 Final Report. Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period. June 21, 2007.</p> <p><b>Sub-chronic and chronic:</b> NOTOX 2007b. Project 484492 Final Draft Report. Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period. October 2007.</p> | --                                                                                                                         |
| Species                                                                                                        | Rat                                                                                                                                                                                                                                                                                                                                                                                                                                          | --                                                                                                                         |
| Target Organ / Effect                                                                                          | Liver, and Thyroid                                                                                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                         |
| Description of TRV endpoints/basis for points of departure (POD)                                               | <p><b>Short-term:</b> Decreased cholesterol</p> <p><b>Subchronic and chronic:</b> Liver weight changes, morphological changes in liver and thyroid gland, decreased TT4, decreased red blood cells, decreased hematocrit and hemoglobin</p>                                                                                                                                                                                                  | --                                                                                                                         |

|                                        |                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                              |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other Endpoints                        | <p><b>Short-term</b> “co-critical effects”:<br/>Increased relative thyroid weight, decreased serum total thyroxine (TT4), decreased dialysis free thyroxine (dFT4)</p> <p><b>Subchronic and chronic</b> “co-critical effects”:<br/>Increased relative thyroid weight, decreased serum TT4 and dFT4, decreased cholesterol, delayed eye opening</p> | --                                                                                                                                                                                                                           |
| Uncertainty Factors                    | <p><b>Short-term:</b> Total UF =<br/><math>3 \times 3 = 100</math></p> <p><b>Subchronic and chronic:</b> Total UF =<br/><math>3 \times 10 \times 10 = 300</math></p>                                                                                                                                                                               | <p><b>Short-term:</b><br/>Interspecies TD UF = 3<br/>Intraspecies UF = 10<br/>Database UF = 3</p> <p><b>Subchronic and chronic:</b><br/>Interspecies TD UF = 3<br/>Intraspecies Variability UF = 10<br/>Database UF = 10</p> |
| POD Method                             | <p><b>Short-term:</b> BMDL<sub>1SD</sub></p> <p><b>Subchronic and Chronic:</b> NOAEL</p>                                                                                                                                                                                                                                                           | <p><b>Short-term:</b> BMDL<sub>1SD</sub> = 3.01 mg/kg/day</p> <p><b>Subchronic and Chronic</b> NOAEL = 6.9 mg/kg/day</p>                                                                                                     |
| Human Equivalent Concentration in TRV? | <p>HED = POD / DAF<br/>Where DAF = Dose Adjustment Factor</p> <p><b>Short-term:</b><br/><math>POD_{HED} = (3.01 \text{ mg/kg/day}) / 8 = 0.38 \text{ mg/kg/day}</math></p> <p><b>Sub-chronic/chronic:</b><br/><math>POD_{HED} = (6.9 \text{ mg/kg/day}) / 8 = 0.86 \text{ mg/kg/day}</math></p>                                                    | <p>DAF = <math>t_{1/2\text{Human}} / t_{1/2\text{MaleRat}}</math><br/>= 72 hours / 9.22 hours<br/>= 8</p>                                                                                                                    |
| Duration of exposure                   | <p><b>Short-term:</b> 28 day</p> <p><b>Sub-chronic/Chronic:</b> 90 day</p>                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                                                           |
| Time Adjustment in TRV?                | No                                                                                                                                                                                                                                                                                                                                                 | “Dose Adjustment Factor” used based on relative half-life in humans and rats.                                                                                                                                                |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                               |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Developmental or Reproductive Effects? | Developmental                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | MDH 2018; Developmental delays were observed in offspring of mice exposed during pregnancy. This effect was observed at 2-fold higher than the human equivalent dose, upon which the short-term RfD is based. |
| Oral to inhalation extrapolation       | Yes (see below)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                               |
| Additional notes                       | <p>RAA = RfD (mg/kg-d) x Route-to-route scaling factor (kg/m<sup>3</sup>-d) x (1000 µg/mg)<br/>RfD = HED / Total UF</p> <p><b>Short-Term RAA:</b><br/>RfD = 0.0038 (mg/kg/day)<br/>RAA = 0.0038 (mg/kg/day) x (70 kg/20 m<sup>3</sup>/day) x (1000 µg/mg) = 13.3 µg/m<sup>3</sup><br/>rounded to 10 µg/m<sup>3</sup></p> <p><b>Subchronic and Chronic RAA:</b><br/>RfD = 0.0029 (mg/kg/day)<br/>RAA = 0.0029 (mg/kg/day) x (70 kg/20 m<sup>3</sup>/day) x (1000 µg/mg) = 10.2 µg/m<sup>3</sup><br/>rounded to 10 µg/m<sup>3</sup></p>                                                                                                      |                                                                                                                                                                                                               |
| Links to TRV Sources                   | <p><a href="https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfba.pdf">https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfba.pdf</a></p> <p>Short-term:<br/><a href="https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NHEERL&amp;dirEntryId=237924">https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NHEERL&amp;dirEntryId=237924</a></p> <p>Subchronic and chronic: NOTOX 2007b. Project 484492 Final Draft Report. Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period. October 2007.</p> |                                                                                                                                                                                                               |

#### 4.5.2. Texas TCEQ

TABLE 26. TEXAS TCEQ RfC FOR PFBA (CAS 375-73-5)

| Variable                                                                                                       | Value                 | Comment                   |
|----------------------------------------------------------------------------------------------------------------|-----------------------|---------------------------|
| RfC                                                                                                            | 3.5 µg/m <sup>3</sup> | --                        |
| Date                                                                                                           | February 14, 2023     | --                        |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study        | RfC derived from oral RfD |

|                                                                   |                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | Butenhoff JL, Bjork JA, Chang S, Ehresman DJ, Parker GA, Das K, Lau C, Lieder PH, van Otterdijk FM, Wallace KB. 2012. Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies. <i>Reprod Toxicol</i> 33:513-530. | TCEQ references USEPA 2022 tox assessment, which cites Buttenhoff 2012                                                                                                                                                                                                                                                       |
| Species                                                           | Rats                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                                                                                                                                                           |
| Target Organ                                                      | Liver, Thyroid                                                                                                                                                                                                                                                               | --                                                                                                                                                                                                                                                                                                                           |
| Description of TRV endpoints/ basis for points of departure (POD) | Increased relative liver weight (i.e., liver hypertrophy) and decreased thyroxine (T4) in adult male rats                                                                                                                                                                    | --                                                                                                                                                                                                                                                                                                                           |
| Other Endpoints                                                   | Human health hazards of potential concern (liver, thyroid, developmental toxicity), hepatocellular hypertrophy and increased relative liver weight (i.e., liver hypertrophy) and decreased thyroxine (T4) in adult male rats                                                 | --                                                                                                                                                                                                                                                                                                                           |
| Uncertainty Factors                                               | $3 \times 10 \times 10 \times 3 = 1000$                                                                                                                                                                                                                                      | 3 for interspecies TK and TD differences<br>10 for intrahuman variability,<br>10 for subchronic to chronic, and<br>3 for significant database insufficiencies                                                                                                                                                                |
| POD Method                                                        | NOAEL                                                                                                                                                                                                                                                                        | NOAEL = 6 mg/kg-day PFBA ammonium salt                                                                                                                                                                                                                                                                                       |
| Human Equivalent Concentration in TRV?                            | POD <sub>HED</sub> of 1.15 mg/kg-day and 1.27 mg/kg-day for liver hypertrophy and decreased T4, respectively.                                                                                                                                                                | After converting the PODs from units of mg/kg-day PFBA ammonium salt to units of mg/kg-day PFBA (by multiplying by the ratio of the molecular weights of the free acid and the ammonium salt), the ratio of serum clearance values between rats and humans was used to account for toxicokinetic differences between species |
| Duration of exposure                                              | 28 day and 90 days                                                                                                                                                                                                                                                           | --                                                                                                                                                                                                                                                                                                                           |
| Time Adjustment in TRV?                                           | Not explicit in calculation                                                                                                                                                                                                                                                  | UF of subchronic to chronic applied.                                                                                                                                                                                                                                                                                         |
| Developmental or Reproductive Effects?                            | Developmental                                                                                                                                                                                                                                                                | Citing EPA IRIS assessment                                                                                                                                                                                                                                                                                                   |

|                                  |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral to inhalation extrapolation | <p>PFBA RfD = 1.15 and 1.27 mg/kg/day / (3 x 10 x 10 x 3) = 1.0E-03 mg/kg/day</p> <p>Using PFBA RfD = 1.0E-03 mg/kg/day:<br/> PFBA RfC = 1.0E-03 mg/kg/day x 70 kg / 20 m<sup>3</sup>/day = 3.5E-03 mg/m<sup>3</sup> = 3.5 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |
| Additional notes                 | --                                                                                                                                                                                                                                                                                                                                                            |
| Links to TRV Sources             | <a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a>                                                                                                                                                                                                                       |

#### 4.6. Perfluorobutane Sulfonic Acid (PFBS) (CAS 375-73-5)

ERG identified non-carcinogenic health-based screening values for PFBS. The identified values come from Minnesota and Texas and range from 0.3 to 4.9 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental or reproductive effects were not observed for PFBS in TRV documentation. However, [ATSDR's 2022 Toxicological Profile](#) noted developmental effects across multiple studies including decreases in pup body weight, delays in eye opening, vaginal opening, and first estrous (York 2002, 2003a); and reproductive and endocrine effects in offspring (Feng et al. 2017).

PFBS is not present on the DOT list of inhalation hazards.

**TABLE 27. INHALATION TRVs FOR PERFLUOROBUTANE SULFONIC ACID (PFBS) (CAS 375-73-5)**

| State/Agency | TRV             | TRV                   | Classification          | DEQ Notes                        |
|--------------|-----------------|-----------------------|-------------------------|----------------------------------|
| Minnesota DH | Short-term RAA  | 0.3 µg/m <sup>3</sup> | Non-cancer, acute       | Unmodified                       |
|              | Sub-chronic RAA | 0.3 µg/m <sup>3</sup> | Non-cancer, sub-chronic | Not needed because same as acute |
|              | Chronic RAA     | 0.3 µg/m <sup>3</sup> | Non-cancer, chronic     | Not needed because same as acute |
| Texas TCEQ   | RfC             | 4.9 µg/m <sup>3</sup> | Non-cancer, chronic     | Not selected – see notes below   |

DEQ proposes Minnesota's value over TCEQ despite an older publication date because it: 1- is based on a more recent critical study than the TCEQ value, 2- has more transparent derivation calculations, 3- is based on a study that is closer to matching DEQ's 24-hour averaging time, 4- has lower uncertainty factors (100 vs. 300), 5- is based on the preferred benchmark dose modeling for POD rather than a NOAEL.



#### 4.6.1. Minnesota DH

TABLE 28. MINNESOTA DH RAA FOR PFBS (CAS 375-73-5)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                             | Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Short-term Non-Cancer RAA                                                                                      | 0.3 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                             | Short-term (>24 hours; < 30 days).                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Sub-chronic Non-Cancer RAA                                                                                     | 0.3 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                             | Sub-chronic (>30 days and <10% of lifetime);<br><br>The calculated MDH subchronic RfD (0.00054 mg/kg-d) results in RAA (2 µg/m <sup>3</sup> ) that is higher than the short-term RAA (0.3 µg/m <sup>3</sup> ) which is based on thyroid effects. The RAA must be protective of shorter duration exposures that occur within the subchronic period and therefore, the subchronic RAA is set equal to the short-term RAA of 0.3 µg/m <sup>3</sup> (MDH 2001, 2008). |
| Chronic Non-Cancer RAA                                                                                         | 0.3 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                             | Chronic (>10% of lifetime);<br><br>The calculated MDH chronic RfD (0.00018 mg/kg-d) results in RAA (0.6 µg/m <sup>3</sup> ) that is higher than the short-term RAA (0.3 µg/m <sup>3</sup> ) which is based on thyroid effects. The chronic RAA must be protective of shorter duration exposures that occur within the chronic period and therefore, the chronic RAA is set equal to the short-term RAA of 0.3 µg/m <sup>3</sup> (MDH 2001, 2008).                 |
| Date                                                                                                           | August 2022                                                                                                                                                                                                                                                                                       | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                                                                                                                                                                                                                                                                                    | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Critical study                                                                                                 | National Toxicology Program (NTP). 2019. "Toxicity studies of perfluoroalkyl sulfonates administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats (TOX-96)." from <a href="https://cebs.niehs.nih.gov/cebs/publication/TOX-96">https://cebs.niehs.nih.gov/cebs/publication/TOX-96</a> | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                                                                  |                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Species                                                          | Rat                                                                                                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Target Organ / Effect                                            | Thyroid                                                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Description of TRV endpoints/basis for points of departure (POD) | Decreased total T4                                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Other Endpoints                                                  | --                                                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Uncertainty Factors                                              | Total UF =<br>3 x 3 x 10 = 100                                                                                                    | Interspecies TD UF = 3<br>Intraspecies Variability UF = 10<br>Database UF = 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| POD Method                                                       | BMDL <sub>1SD</sub> = 6.97 mg/kg/day                                                                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Human Equivalent Concentration in TRV?                           | HED = POD * DAF<br>Where DAF = Dose Adjustment Factor<br><br>POD <sub>HED</sub> = (6.97 mg/kg/day) x<br>0.0012 = 0.0084 mg/kg/day | Chemical- and Study-Specific<br>Toxicokinetic Adjustment<br><br>DAF = t <sub>1/2</sub> Female Rat/ t <sub>1/2</sub> Human<br>= 1.3 hours / 1050 hours<br>= 0012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Duration of exposure                                             | 28-day                                                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Time Adjustment in TRV?                                          | No                                                                                                                                | "Dose Adjustment Factor" used based on relative half-life in humans and rats.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Developmental or Reproductive Effects?                           | Developmental and Reproductive                                                                                                    | MDH 2022; Two oral developmental studies (one in rats and one in mice) and a 2-generation study in rats have been conducted. The developmental effects reported in the mouse study included decreased pup body weight, decreased serum thyroid hormones, delayed eye opening, delayed vaginal opening and first estrus as well as smaller ovarian and uterine size in adult offspring<br><br>MDH 2022; Researchers examined the association between PFAS chemicals and endometriosis related infertility among Chinese reproductive-age women in a case-control study. Women with endometriosis-related infertility had significantly higher median levels of PFBS compared with those without the disease |
| Oral to inhalation extrapolation                                 | Yes (see below)                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | $RAA = RfD \text{ (mg/kg-d)} \times \text{Route-to-route scaling factor (kg/m}^3\text{-d)} \times (1000 \text{ } \mu\text{g/mg})$ $RfD = HED / \text{Total UF}$ <p><b>Short-Term RAA:</b><br/> <math display="block">RfD = 0.000084 \text{ (mg/kg/day)}</math> <math display="block">RAA = 0.000084 \text{ (mg/kg/day)} \times (70 \text{ kg}/20 \text{ m}^3\text{/day)} \times (1000 \text{ } \mu\text{g/mg}) = 0.29 \text{ } \mu\text{g/m}^3 \text{ rounded to } 0.3 \text{ } \mu\text{g/m}^3</math></p> |
| Links to TRV Sources | <a href="https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfbs.pdf">https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfbs.pdf</a>                                                                                                                                                                                                                                                                                                                |

#### 4.6.2. Texas TCEQ

TABLE 29. TEXAS TCEQ RfC FOR PFBS (CAS 375-73-5)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                       | Comment                                                                                      |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| RfC                                                                                                            | 4.9 $\mu\text{g/m}^3$                                                                                                                                                                                                                                                                                                                                                       | --                                                                                           |
| Date                                                                                                           | February 14, 2023                                                                                                                                                                                                                                                                                                                                                           | --                                                                                           |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                                                                                                                                                                                                                                                                                                                                                              | RfC derived from oral RfD                                                                    |
| Critical study                                                                                                 | <p>Leider PH, SC Chang, RG York, JL Butenhoff. 2009. Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats. Toxicology 255:45-52.</p> <p>York RG 2003. Oral (Gavage) Repeated Dose 90-Day Toxicity Study of Potassium Perfluorobutane Sulfonate (PFBS) in Rats. Argus Research Protocol Number 418-026.</p> | TCEQ references Minnesota Department of Health, which cites Leider et al. 2009 and York 2003 |
| Species                                                                                                        | Rats                                                                                                                                                                                                                                                                                                                                                                        | --                                                                                           |
| Target Organ                                                                                                   | Blood, Kidney                                                                                                                                                                                                                                                                                                                                                               | --                                                                                           |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Decreased hemoglobin and hematocrit, and histological changes in the kidney                                                                                                                                                                                                                                                                                                 | --                                                                                           |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                          | --                                                                                           |

|                                           |                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                               |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Uncertainty Factors                       | $1 \times 10 \times 3 \times 10 = 300$                                                                                                                                                                                                                                                                                                                     | 1 for interspecies TD differences<br>10 for intrahuman variability,<br>3 for subchronic to chronic, and<br>10 for significant database<br>insufficiencies (i.e., only one study<br>available) |
| POD Method                                | NOAEL                                                                                                                                                                                                                                                                                                                                                      | NOAEL = 60 mg/kg-day                                                                                                                                                                          |
| Human Equivalent<br>Concentration in TRV? | HED = 0.42 mg/kg-day                                                                                                                                                                                                                                                                                                                                       | Obtained by Minnesota Department<br>of Health using a TK interspecies<br>factor of 142 (for extrapolation from<br>males to humans; detailed<br>calculation not provided)                      |
| Duration of exposure                      | 90 days                                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                                                                                            |
| Time Adjustment in<br>TRV?                | Not explicit in calculation                                                                                                                                                                                                                                                                                                                                | UF of subchronic to chronic applied.                                                                                                                                                          |
| Developmental or<br>Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                            |
| Oral to inhalation<br>extrapolation       | PFBS RfD = 60 mg/kg/day / (142 x 1 x 10 x 3 x 10) = 1.4E-03 mg/kg/day<br><br>Using PFBS RfD = 1.4E-03 mg/kg/day:<br>PFBS RfC = 1.4E-03 mg/kg/day x 70 kg / 20 m <sup>3</sup> /day = 4.9E-03 mg/m <sup>3</sup> = 4.9<br>µg/m <sup>3</sup><br><br>Where the human adult body weight is 70 kg, and the human daily<br>ventilation volume is 20 m <sup>3</sup> |                                                                                                                                                                                               |
| Additional notes                          | --                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                               |
| Links to TRV Sources                      | <a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a>                                                                                                                                                                                                                    |                                                                                                                                                                                               |

#### 4.7. Perfluorohexanoic acid (PFHxA) (CAS 307-24-4)

ERG identified non-carcinogenic health-based screening values for PFHxA. The identified values come from Minnesota and range from 0.5 to 1 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental and reproductive effects were cited for PFHxA in multiple TRV source documents. In addition, [ATSDR's 2022 Toxicological Profile](#) found multiple studies with developmental or reproductive effects including an inverse association for testosterone levels in adolescent boys (Zhou et al. 2016); and decreases in fetal weight in rats (Loveless et al. 2009).

PFHxA is not present on the DOT list of inhalation hazards.

**TABLE 30. TRVS FOR PERFLUOROHEXANOIC ACID (PFHxA) (CAS 307-24-4)**

| State/Agency | TRV             | TRV                   | Classification          | DEQ Notes                 |
|--------------|-----------------|-----------------------|-------------------------|---------------------------|
| Minnesota DH | Short-term RAA  | 1 µg/m <sup>3</sup>   | Non-cancer, acute       | Unmodified                |
|              | Sub-chronic RAA | 0.5 µg/m <sup>3</sup> | Non-cancer, sub-chronic | No analogous TRV category |
|              | Chronic RAA     | 0.5 µg/m <sup>3</sup> | Non-cancer, chronic     | Unmodified                |

No other options to choose from.

#### 4.7.1. Minnesota DH

TABLE 31. MINNESOTA DH SHORT-TERM AND LONG-TERM RAA VALUE FOR PFHXA (CAS 307-24-4)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Comment                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-Cancer Short-term RAA                                                                                      | 1 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Short-term (>24 hours; < 30 days)                                                                                                                |
| Non-Cancer Subchronic and Chronic RAA                                                                          | 0.5 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Sub-chronic (> 30days and <10% of lifetime) and chronic (>10% of lifetime) have the same RAA value of 0.5 µg/m <sup>3</sup> and same derivation. |
| Date                                                                                                           | February 2022                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | --                                                                                                                                               |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat studies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | All three are based on RfDs from oral rat studies.                                                                                               |
| Critical study                                                                                                 | <p><b>Short-term:</b> National Toxicology Program (NTP). 2019. 28-Day Evaluation of the Toxicity (C20613) of Perfluorohexanoic acid (PFHXA) (307-24-4) in Harlan Sprague-Dawley Rats Exposed via Gavage. Study tables retrieved from <a href="https://cebs.niehs.nih.gov/cebs/publication/TOX-97">https://cebs.niehs.nih.gov/cebs/publication/TOX-97</a></p> <p><b>Subchronic/chronic:</b> Loveless, S. E., Slezak, B., Serex, T., Lewis, J., Mukerji, P., O'Connor, J. C., . . . Buck, R. C. 2009. Toxicological evaluation of sodium perfluorohexanoate. Toxicology, 264(1-2), 32-44. doi:10.1016/j.tox.2009.07.011</p> | --                                                                                                                                               |
| Species                                                                                                        | Rat                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | --                                                                                                                                               |
| Target Organ / Effect                                                                                          | <p><b>Short-term:</b> Thyroid</p> <p><b>Subchronic/chronic:</b> Liver</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | --                                                                                                                                               |
| Description of TRV endpoints/basis for points of departure (POD)                                               | <p><b>Short-term:</b> Decreased total T4</p> <p><b>Subchronic/chronic:</b> Nasal epithelium degeneration</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                                                               |

|                                        |                                                                                                                                                                                                                                                                                |                                                                                                                                                                        |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other Endpoints                        | <b>Short-term</b> “Co-critical effects”:<br>Decreased pup body weight<br><br><b>Subchronic/chronic</b> “Co-critical effects”:<br>Decreased bilirubin                                                                                                                           | --                                                                                                                                                                     |
| Uncertainty Factors                    | <b>For short-term and subchronic/chronic RfD:</b><br>$(3 \times 10 \times 10) = 300$                                                                                                                                                                                           | UF (animal to human) = 3<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 10                                                                            |
| POD Method                             | <b>Short-term:</b> BMDL <sub>1SD</sub><br><br><b>Subchronic/chronic:</b> BMDL <sub>10%</sub>                                                                                                                                                                                   | <b>Short-term:</b><br>BMDL <sub>1SD</sub> = 25.9 mg/kg/day<br><br><b>Subchronic and chronic:</b><br>BMDL <sub>10%</sub> = 22.5 mg/kg/day                               |
| Human Equivalent Concentration in TRV? | HED = POD x DAF<br>Where DAF = Dose Adjustment Factor<br><br><b>Short-term:</b><br>$POD/DAF = 25.9 \text{ mg/kg/day} \times 0.0037 = 0.0958 \text{ mg/kg/day}$<br><br><b>Subchronic/Chronic:</b><br>$POD/DAF = 22.5 \text{ mg/kg/day} \times 0.0020 = 0.045 \text{ mg/kg/day}$ | Chemical and Study-Specific Toxicokinetic Adjustment<br><br>$DAF = t_{1/2\text{Human}} / t_{1/2\text{MaleRat}}$<br>$= 2.87 \text{ hrs} / 768 \text{ hrs}$<br>$= .0037$ |
| Duration of exposure                   | <b>Short-term:</b> 28 days<br><br><b>Subchronic/chronic:</b> 90 days; for reproductive subset dosed for 70 days prior to cohabitation                                                                                                                                          | --                                                                                                                                                                     |
| Time Adjustment in TRV?                | No                                                                                                                                                                                                                                                                             | “Dose Adjustment Factor” used based on relative half-life in humans and rats.                                                                                          |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Developmental or Reproductive Effects? | Developmental and reproductive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <p>MDH 2021; Decreases in pup body weight and increased pup mortality have been reported. These effects were observed at levels ~1500-fold higher than the subchronic/chronic RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of a two-generation study</p> <p>MDH 2021; Significant decreases in maternal body weight gain during gestation and complete litter loss were reported at doses &gt;3,000-fold higher than the subchronic/chronic RfD. Decreases in sperm count and seminiferous tubule spermatid retention were reported at doses 25,000-fold higher than the Subchronic/Chronic RfD.</p> |
| Oral to inhalation extrapolation       | Yes (see below)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Additional notes                       | <p>RAA = RfD (mg/kg-d) x Route-to-route scaling factor (kg/m<sup>3</sup>-d) x (1000 µg/mg)<br/>RfD = HED / Total UF</p> <p><b>Short-term:</b><br/>HED/Total UF = 0.0958/300 = 0.00032 mg/kg/day (laboratory animal – SD rats)<br/>RfD = 0.00032 mg/kg/day<br/>RAA = 0.00032 (mg/kg/day) x (70 kg/20 m<sup>3</sup>/day) x (1000 µg/mg) = 1.12 µg/m<sup>3</sup> = 1 µg/m<sup>3</sup></p> <p><b>Subchronic/Chronic:</b><br/>HED/Total UF = 0.045/300 = 0.00015 mg/kg/day (laboratory animal – SD rats)<br/>RfD = 0.00015 mg/kg/day<br/>RAA = 0.00015 (mg/kg/day) x (70 kg/20 m<sup>3</sup>/day) x (1000 µg/mg) = 0.525 µg/m<sup>3</sup> rounded to 0.5 µg/m<sup>3</sup></p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfhxa.pdf">https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfhxa.pdf</a><br><br>Short-term: <a href="https://cebs.niehs.nih.gov/cebs/publication/TOX-97">https://cebs.niehs.nih.gov/cebs/publication/TOX-97</a><br><br>Subchronic/chronic:<br><a href="https://www.sciencedirect.com/science/article/abs/pii/S0300483X09003680">https://www.sciencedirect.com/science/article/abs/pii/S0300483X09003680</a> |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.8. Perfluorohexanesulphonic acid (PFHxS) (CAS 355-46-4)

ERG identified non-carcinogenic health-based screening values for PFHxS. The identified values come from Minnesota and Texas and range from 0.013 to 0.034  $\mu\text{g}/\text{m}^3$ . Cancer screening values were not identified.

Developmental or reproductive effects were not cited in the TRV source documentation for PFHxS. However, [ATSDR's 2022 Toxicological Profile](#) found multiple epidemiological studies with developmental or reproductive effects including associations with risk of preterm births among women; decreased birth weight; adiposity at birth; birth length; and neurodevelopmental outcomes in children. The Toxicological Profile also cited developmental or reproductive effects for numerous laboratory animal studies.

PFHxS is not present on the DOT list of inhalation hazards.

**TABLE 32. INHALATION TRVs FOR PERFLUOROHEXANESULPHONIC ACID (PFHxS) (CAS 355-46-4)**

| State/Agency | TRV Type        | TRV Value                      | Classification          | DEQ Notes                                                 |
|--------------|-----------------|--------------------------------|-------------------------|-----------------------------------------------------------|
| Minnesota DH | RAA short-term  | 0.034 $\mu\text{g}/\text{m}^3$ | Non-cancer, acute       | Unmodified                                                |
|              | RAA sub-chronic | 0.034 $\mu\text{g}/\text{m}^3$ | Non-cancer, sub-chronic | Not needed because same as acute                          |
|              | RAA chronic     | 0.034 $\mu\text{g}/\text{m}^3$ | Non-cancer, chronic     | Not needed because same as acute                          |
| Texas TCEQ   | RfC             | 0.013 $\mu\text{g}/\text{m}^3$ | Non-cancer, long-term   | Derived from much older tox study than Minnesota DH value |



#### 4.8.1. Minnesota DH

TABLE 33. MINNESOTA DH RAA VALUE FOR PFHxS (CAS 355-46-4)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                          | Comment                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-Cancer Risk Assessment Advice Value (RAA)                                                                  | 0.034 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                        | Short-term (>24 hours; < 30 days), sub-chronic (>30days and <10% of lifetime), and chronic (>10% of lifetime) all have the same value of 0.034 µg/m <sup>3</sup> and same derivation. |
| Date                                                                                                           | August 2021                                                                                                                                                                                                                                                                                                                    | --                                                                                                                                                                                    |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                                                                                                                                                                                                                                                                                                                 | --                                                                                                                                                                                    |
| Critical study                                                                                                 | National Toxicology Program (NTP). 2018. TOX-96: Toxicity Report Tables and Curves for Short-term Studies: Perfluorinated Compounds: Sulfonates. <a href="https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&amp;bin_id=3874">https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&amp;bin_id=3874</a> | --                                                                                                                                                                                    |
| Species                                                                                                        | Rats                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                                                    |
| Target Organ / Effect                                                                                          | Thyroid and Liver                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                       |
| Description of TRV endpoints/basis for points of departure (POD)                                               | Decreased free T4                                                                                                                                                                                                                                                                                                              | --                                                                                                                                                                                    |
| Other Endpoints                                                                                                | 'Co-critical effects': Decreased free and total T4, triiodothyronine (T3), and changes in cholesterol levels and increased hepatic focal necrosis                                                                                                                                                                              | --                                                                                                                                                                                    |
| Uncertainty Factors                                                                                            | Total UF = 3 x 10 x 10 = 300                                                                                                                                                                                                                                                                                                   | Interspecies TD UF = 3<br>Intraspecies Variability UF = 10<br>Database UF = 10                                                                                                        |
| POD Method                                                                                                     | BMDL <sub>20%</sub>                                                                                                                                                                                                                                                                                                            | 32.4 µg/mL (or mg/L) serum concentration                                                                                                                                              |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                       |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | $HED = POD \times DAF$<br>Where DAF = Dose Adjustment Factor<br><br>$HED = 32.4 \text{ mg/L} \times 0.000090 \text{ L/kg-d} = 0.00292 \text{ mg/kg-d}$                                                                                                                                                                                                                             | Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) $\times$ (Ln2/Half-life, days) = $0.25 \text{ L/kg} \times (0.693/1935 \text{ days}) = 0.000090 \text{ L/kg-day}$ . (Half-life from Li et al 2018) |
| Duration of exposure                   | 28 days                                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                                                                                                                                                    |
| Time Adjustment in TRV?                | Yes                                                                                                                                                                                                                                                                                                                                                                                | "Dose Adjustment Factor" used based on relative half-life in humans and rats.                                                                                                                                                                         |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                 | Tested for but not observed.                                                                                                                                                                                                                          |
| Oral to inhalation extrapolation       | Yes                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                       |
| Additional notes                       | $RAA = RfD \text{ (mg/kg-d)} \times \text{Route-to-route scaling factor (kg/m}^3\text{-d)} \times (1000 \text{ }\mu\text{g/mg})$<br>$RfD = HED / \text{Total UF}$<br><br>$RfD = 0.0000097 \text{ mg/kg/day}$<br>$RAA = 0.0000097 \text{ (mg/kg/day)} \times (70 \text{ kg}/20 \text{ m}^3\text{/day)} \times (1000 \text{ }\mu\text{g/mg}) = 0.034 \text{ }\mu\text{g/m}^3$        |                                                                                                                                                                                                                                                       |
| Links to TRV Sources                   | <a href="https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfhxs.pdf">https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfhxs.pdf</a><br><br><a href="https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&amp;bin_id=3874">https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&amp;bin_id=3874</a> |                                                                                                                                                                                                                                                       |

#### 4.8.2. Texas TCEQ

TABLE 34. TEXAS TCEQ RfC FOR PFHXS (CAS 355-46-4)

| Variable                                                                                                       | Value                           | Comment                   |
|----------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------|
| RfC                                                                                                            | $0.013 \text{ }\mu\text{g/m}^3$ | --                        |
| Date                                                                                                           | February 14, 2023               | --                        |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                  | RfC derived from oral RfD |

|                                                                   |                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | Hoberman AM, York RG. 2003. Oral (gavage) combined repeated dose toxicity study of T-7706 with the reproduction/developmental toxicity screening test. Argus Research. | TCEQ references ATSDR 2009 tox profile, which cites Hoberman and York 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Species                                                           | Rats                                                                                                                                                                   | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Target Organ                                                      | Hematological changes                                                                                                                                                  | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Description of TRV endpoints/ basis for points of departure (POD) | Significantly decreased hemoglobin concentration, decreased erythrocyte count and decreased hematocrit                                                                 | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Other Endpoints                                                   | Hypertrophy-hyperplasia of thyroid follicular cells                                                                                                                    | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Uncertainty Factors                                               | For RfD:<br>Total UF = $263 \times 1 \times 3 \times 10 \times 10 = 78900$                                                                                             | Interspecies TK UF = 263<br>Interspecies TD UF = 1<br>LOAEL to NOAEL = 3<br>Intrahuman UF = 10<br>Database UF (data insufficiency) = 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| POD Method                                                        | LOAEL                                                                                                                                                                  | LOAEL of 0.3 mg/kg/day for hematology findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Human Equivalent Concentration in TRV?                            | Interspecies UF of 263                                                                                                                                                 | TCEQ used "a data-based TK interspecies extrapolation factor available for an 8-carbon PFAS (PFOS) as a surrogate for the 6-carbon PFHxS. This appears reasonable based on available half-life data since the human half-life for PFOS (1,053-2,701 days) is most similar to that for PFHxS (2,662 days) among PFAS with reported human half-lives (Table 3-8 of ATSDR 2009). Therefore, to derive an RfD for a chemical that may otherwise go unaddressed at a site, TCEQ will assume the ratio of human-to-rat half-lives for PFHxS is the same as that of PFOS, maintaining the human-to-rat half-life ratio of approximately 263" |
| Duration of exposure                                              | Daily oral exposure from pre mating to post-natal day 21 (females)                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Time Adjustment in TRV?                                           | No                                                                                                                                                                     | Not explicit in calculation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Developmental or Reproductive Effects?                            | No significant developmental or reproductive effects                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Oral to inhalation extrapolation                                  | Yes (see below)                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|                      |                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | <p>PFHxS RfD = 0.3 mg/kg/day / (263 x 1 x 3 x 10 x 10) = 3.8E-06 mg/kg/day = 0.0038 µg/m<sup>3</sup></p> <p>Using RfD = 3.8E-06 mg/kg/day:<br/>PFHxS RfC = 3.8E-06 mg/kg/day x 70 kg/20 m<sup>3</sup>/day = 1.3E-05 mg/m<sup>3</sup> = 0.013 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |
| Links to TRV Sources | <p><a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a></p> <p>TAMIS database:<br/><a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a></p>                                               |

#### 4.9. Perfluorooctanoic acid (PFOA) (CAS 335-67-1)

ERG identified non-carcinogenic health-based screening values for PFOA. The identified values come from seven different state agencies and range from 0.005 to 0.063 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental and reproductive effects were observed for PFOA in various TRV source documents. In addition, [ATSDR's 2022 Toxicological Profile](#) found multiple epidemiological studies with developmental or reproductive effects including associations with effects on reproductive hormone levels, sperm, menstrual cycle length, menopause onset, endometriosis, breastfeeding duration, fertility, pregnancy outcomes, birth outcomes, neurodevelopmental outcomes, and development of the reproductive system. The Toxicological Profile also cites developmental or reproductive effects for numerous laboratory animal studies.

PFOA is not present on the DOT list of inhalation hazards.

TABLE 35. INHALATION TRVs FOR PFOA (CAS 335-67-1)

| State/Agency       | TRV          | TRV                      | Classification          | DEQ Notes                                                  |
|--------------------|--------------|--------------------------|-------------------------|------------------------------------------------------------|
| Michigan DE        | 24-hour ITSL | 0.0001 µg/m <sup>3</sup> | Non-cancer, acute       | Unmodified except applied as chronic rather than acute TRV |
| Minnesota DH       | RAA          | 0.063 µg/m <sup>3</sup>  | Non-cancer, acute       | Unmodified                                                 |
|                    | RAA          | 0.063 µg/m <sup>3</sup>  | Non-cancer, sub-chronic | Not needed because same as acute                           |
|                    | RAA          | 0.063 µg/m <sup>3</sup>  | Non-cancer, chronic     | Not needed because same as acute                           |
| New Hampshire DES* | 24-Hour AAL  | 0.05 µg/m <sup>3</sup>   | Non-cancer, acute       | Derived from occupational                                  |

|                |                              |                                          |                     |                                               |
|----------------|------------------------------|------------------------------------------|---------------------|-----------------------------------------------|
|                | Annual AAL                   | 0.024 µg/m <sup>3</sup>                  | Non-cancer, chronic | Derived from occupational                     |
| New Jersey DEP | RfC                          | 0.007 µg/m <sup>3</sup>                  | Non-cancer, chronic | Based on older critical study than Michigan   |
| New York DEC   | AGC                          | 0.0053 µg/m <sup>3</sup>                 | Non-cancer, chronic | Based on older critical study than Michigan   |
| Texas TCEQ     | Short-Term ESL               | 0.05 µg/m <sup>3</sup>                   | Non-cancer, acute   | No derivation information available           |
|                | Long-Term ESL                | 0.005 µg/m <sup>3</sup>                  | Non-cancer, chronic | No derivation information available           |
|                | RfC                          | 4.1 x 10 <sup>-3</sup> µg/m <sup>3</sup> | Non-cancer, chronic | Based on inhalation study but very old (1986) |
| Wisconsin DNR* | 24-Hour Ambient Air Standard | 0.24 µg/m <sup>3</sup>                   | Non-cancer, acute   | Derived from occupational                     |

\*Reported for Ammonium perfluorooctanoate (APFO) (CAS # 3825-26-1)

Michigan did not make any quantitative adjustments to their value to make it fit an acute exposure time frame, and the recent (March 2024) EPA oral RfD on which it is based is a chronic RfD. Therefore, DEQ proposes to use the unmodified Michigan value as a chronic, rather than acute, TRV.

#### 4.9.1. Michigan EGL

TABLE 36. MICHIGAN EGLE ITSL FOR PFOA (CAS 335-67-1)

| Variable                                                                                                       | Value                                            | Comment                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| ITSL                                                                                                           | 0.0001 µg/m <sup>3</sup>                         | 24-hour time averaging                                                                                                                  |
| Date                                                                                                           | April 25, 2024                                   | Originally set in February 5, 2018 then updated on April 25, 2024 when EPA updated its final Human Health Toxicity Assessment for PFOA. |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Derived from 2024 EPA oral RfD of 3E-8 mg/kg/day | --                                                                                                                                      |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                            |
|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | <p>Budtz-Jørgensen, E; Grandjean, P. (2018). Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity. PLoS ONE 13: e0205388.<br/><a href="http://dx.doi.org/10.1371/journal.pone.0205388">http://dx.doi.org/10.1371/journal.pone.0205388</a></p> <p>Wikström, S; Hussein, G; Lingroth Karlsson, A; Lindh, CH; Bornehag, CG. (2021). Exposure to perfluoroalkyl substances in early pregnancy and risk of sporadic first trimester miscarriage. Scientific Reports 11: 3568.<br/><a href="http://dx.doi.org/10.1038/s41598-021-82748-6">http://dx.doi.org/10.1038/s41598-021-82748-6</a></p> <p>Dong, Z; Wang, H; Yu, YY; Li, YB; Naidu, R; Liu, Y. (2019). Using 2003-2014 U.S. NHANES data to determine the associations between per- and polyfluoroalkyl substances and cholesterol: Trend and implications. Ecotoxicology and Environmental Safety 173: 461- 468.</p> | --                                                                                                                         |
| Species                                                           | Human                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Epidemiological studies.                                                                                                   |
| Target Organ                                                      | Immune system, developmental, cholesterol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                         |
| Description of TRV endpoints/ basis for points of departure (POD) | Decreased serum anti-tetanus and anti-diphtheria antibody concentrations in children (Budtz-Jørgensen and Grandjean, 2018), decreased infant birth weight (Wikström et al., 2020), and increased total cholesterol in adults (Dong et al., 2019).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                         |
| Other Endpoints                                                   | Many other effects in toxicity assessment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                         |
| Uncertainty Factors                                               | EGLE did not apply UFs to TRV calculation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | EPA applied uncertainty factors when deriving the oral RfD, but EGLE did not apply uncertainty factors in its calculation. |
| POD Method                                                        | EGLE used an oral RfD to RfC conversion;                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | EPA used benchmark dose modeling (BMDL) to derive multiple oral RfDs                                                       |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                         |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | Yes in EPA oral RfD derivation.                                                                                                                                                                                                                                                                                                                                                                                                                                                 | --                                                                                                                      |
| Duration of exposure                   | Various                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | --                                                                                                                      |
| Time Adjustment in TRV?                | No (see note)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ITSL is determined for a 24-hour time averaging; however, no explicit time-adjustment is present in the TRV derivation. |
| Developmental or Reproductive Effects? | Developmental and Reproductive in PFOA Toxicity Assessment                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                         |
| Oral to inhalation extrapolation       | $\text{ITSL} = \text{RfD} \times (\text{avg. body weight}) / (\text{inhalation rate per day}) \times \text{unit-conversion}$ $\text{ITSL} = (3\text{E-}8 \text{ mg/kg}) \times (70\text{kg}) / (20\text{m}^3) \times 1000\mu\text{g/mg}$ $\text{ITSL} = 0.000105 \mu\text{g/m}^3 \text{ rounded to } 0.0001 \mu\text{g/m}^3.$ <p>Because the developmental effects of PFOA can occur over short periods of time, pursuant to Rule 232(2)(d) the averaging time is 24 hours.</p> |                                                                                                                         |
| Additional notes                       | Multiple alternative RfC calculations were presented as well as potential ITSLs calculated from an OEL in the original EGLE 2018 source document.                                                                                                                                                                                                                                                                                                                               |                                                                                                                         |
| Links to TRV Sources                   | <a href="https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=335671&amp;cmdSubmit=Submit">https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=335671&amp;cmdSubmit=Submit</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/335-67-1/335-67-1_24hr_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/335-67-1/335-67-1_24hr_ITSL.pdf</a>                                                        |                                                                                                                         |

#### 4.9.2. Minnesota DH

TABLE 37. MINNESOTA DH RAA VALUE FOR PFOA (CAS 335-67-1)

| Variable                                                                                                       | Value                          | Comment                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-Cancer Risk Assessment Advice (RAA)                                                                        | 0.063 $\mu\text{g/m}^3$        | Short-term (>24 hours; < 30 days), Sub-chronic (>30 days and <10% of lifetime), and chronic (>10% of lifetime) all have the same value of 0.063 $\mu\text{g/m}^3$ . Insufficient data to derive an RAA for acute exposure (< 24 hours). |
| Date                                                                                                           | June 2022                      | --                                                                                                                                                                                                                                      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral developmental mouse study | RfD derived by MDH in 2017.                                                                                                                                                                                                             |

|                                                                   |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, Strynar MJ. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci. 2006 Apr;90(2):510-8. doi: 10.1093/toxsci/kfj105. | <a href="#">EPA 2016a</a> predicted average serum concentration for maternal animals from Lau et al 2006).<br><br>Note: EPA 2016a is now out of date.                                                                                                                                                                                                                                                                            |
| Species                                                           | Mouse                                                                                                                                                                                                                       | --                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Target Organ                                                      | Developmental                                                                                                                                                                                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Description of TRV endpoints/ basis for points of departure (POD) | Developmental delay                                                                                                                                                                                                         | Delayed ossification, accelerated preputial separation in male offspring, trend for decreased pup body weight, and increased maternal liver weight                                                                                                                                                                                                                                                                               |
| Other Endpoints                                                   | In offspring exposure during development, researchers observed changes in liver weight, histology, and triglycerides, and delayed mammary gland development in pups.                                                        | In adult animals, researchers observed liver weight changes, liver enzyme levels, changes in triglyceride and cholesterol levels, microscopic evidence of cellular damage and bile duct hyperplasia; decreased spleen weight and spleen lymphocytes; decreased IgM response; kidney weight changes and papilla urothelium hyperplasia; increased pancreatic acinar cell hyperplasia; and decreased serum thyroid hormone levels. |
| Uncertainty Factors                                               | Total UF = 300                                                                                                                                                                                                              | UF (sensitive individuals) = 10<br>UF (animal to human) = 3<br>UF (LOAEL to NOAEL) = 3<br>UF (data insufficiency) = 3                                                                                                                                                                                                                                                                                                            |
| POD Method                                                        | LOAEL                                                                                                                                                                                                                       | LOAEL of 0.000018 mg/kg/day for adverse developmental effects                                                                                                                                                                                                                                                                                                                                                                    |
| Human Equivalent Concentration in TRV?                            | Yes                                                                                                                                                                                                                         | HED = POD x DAF = 38 mg/L x 0.00014 L/kg/day = 0.0053 mg/kg-d<br><i>Where DAF is dose adjustment factor</i><br><br>RfD = HED/UF = 0.0053/300 = 0.000018 mg/kg-d                                                                                                                                                                                                                                                                  |
| Duration of exposure                                              | Gestation days 1 to 17                                                                                                                                                                                                      | -                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Time Adjustment in TRV?                                           | Yes                                                                                                                                                                                                                         | -                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Developmental or Reproductive Effects?                            | Developmental                                                                                                                                                                                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                               |



|                                  |                                                                                                                                                                                                                                                                                                                            |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral to inhalation extrapolation | <p>RfD = 0.000018 mg/kg/day</p> <p>RAA = RfD * oral-inhalation scaling factor * unit conversion</p> <p>RAA = 0.000018 (mg/kg/day) x (70 kg/20 m<sup>3</sup>/day) x (1000 µg/mg) = 0.063 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |
| Additional notes                 | --                                                                                                                                                                                                                                                                                                                         |
| Links to TRV Sources             | <p><a href="https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfoa.pdf">https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfoa.pdf</a></p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/16415327/">https://pubmed.ncbi.nlm.nih.gov/16415327/</a></p>                |

### 4.9.3. New Hampshire DES

**TABLE 38. NEW HAMPSHIRE DES 24-HOUR AND ANNUAL AAL FOR AMMONIUM PERFLUOROOCTANOATE (APFO) (CAS 3825-26-1)**

| Variable                                                                                                       | Value                                                                               | Comment                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24-Hour AAL                                                                                                    | 0.05 µg/m <sup>3</sup>                                                              | 24-hour ambient air limit                                                                                                                                                                                                                                                 |
| Annual AAL                                                                                                     | 0.024 µg/m <sup>3</sup>                                                             | Annual ambient air limit                                                                                                                                                                                                                                                  |
| Date                                                                                                           | --                                                                                  | Unclear when this was established. It was not listed in the most recent changes to regulation in 2022. Found in NHDES presentation in 2017.                                                                                                                               |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit modified with toxicity data from an oral toxicity study | Regulatory approach calls for setting the AAL based on modifying the ACGIH value based on other available toxicity data. See additional notes below.                                                                                                                      |
| Critical study                                                                                                 | ACGIH OEL                                                                           | ACGIH is used as basis of AAL, and unclear what other studies are used to determine acute and chronic toxicity values to set a 'Toxicity Factor' and 'Time Adjustment Factor' to modify the ACGIH value according to the regulatory formula. (See additional notes below) |
| Species                                                                                                        | --                                                                                  | The underlying source for the old ACGIH OEL value used is not available.                                                                                                                                                                                                  |
| Target Organ                                                                                                   | --                                                                                  | --                                                                                                                                                                                                                                                                        |

|                                                                   |                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Description of TRV endpoints/ basis for points of departure (POD) | --                                                                                                                                                                                                                                                                                                                        | --                                                                                                                                                                                                                              |
| Other Endpoints                                                   | --                                                                                                                                                                                                                                                                                                                        | --                                                                                                                                                                                                                              |
| Uncertainty Factors                                               | NH DES refers to a 'Safety Factor (SF)' of 100.<br><br>A time adjustment factor is also applied of 4.2 for the annual AAL and 2 for the 24-hour AAL. (See below).                                                                                                                                                         | New Hampshire assigned APFO a Toxicity Factor = 1 and Time Adjustment Factor = B which correspond to safety factor (SF) = 100 and time adjustment factor (TAF) = 2                                                              |
| POD Method                                                        | OEL                                                                                                                                                                                                                                                                                                                       | OEL = 10 µg/m <sup>3</sup>                                                                                                                                                                                                      |
| Human Equivalent Concentration in TRV?                            | --                                                                                                                                                                                                                                                                                                                        | Not explicit in calculation from OEL.                                                                                                                                                                                           |
| Duration of exposure                                              | --                                                                                                                                                                                                                                                                                                                        | --                                                                                                                                                                                                                              |
| Time Adjustment in TRV?                                           | Yes<br><br>For the Annual AAL, NHDES adjusted the OEL by a factor of 4.2 = 24 hrs per day / 8 hrs per work day) * (7 days per week / 5 days work week)<br><br>For the 24-hour AAL, NHDES assigned 1-methylnaphthalene a 'Time Adjustment Factor (TAF)' based on regulatory criteria 'B,' which corresponds to a TAF of 2. | Annual AAL = OEL / (4.2 * SF)<br>Where: 4.2 = (24 hrs per day / 8 hrs per work day) * (7 days per week / 5 days work week)<br>-----<br>24-Hour AAL = OEL / (SF * TAF)<br><br>SF = safety factor<br>TAF = time adjustment factor |
| Developmental or Reproductive Effects?                            | No                                                                                                                                                                                                                                                                                                                        | No mention of developmental or reproductive effects/studies.                                                                                                                                                                    |
| Oral to inhalation extrapolation                                  | No                                                                                                                                                                                                                                                                                                                        | Not explicit in calculation of TRV from OEL.                                                                                                                                                                                    |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | <p>Calculations of AALs are shown below:</p> <p><u>Annual AAL</u></p> $= \text{OEL} / (4.2 * \text{SF})$ $= 10 \mu\text{g}/\text{m}^3 / (4.2 * 100)$ $= 10 \mu\text{g}/\text{m}^3 / 420$ $= 0.024 / \text{m}^3$ <p>Where: 4.2 = (24 hrs per day / 8 hrs per work day) * (7 days per week / 5 days work week).</p> <p><u>24-hour AAL</u></p> $= \text{OEL} / (\text{SF} * \text{TAF})$ $= 10 \mu\text{g}/\text{m}^3 / (100 * 2)$ $= 10 \mu\text{g}/\text{m}^3 / (200)$ $= 0.05 \mu\text{g}/\text{m}^3$                                                                                                      |
| Links to TRV Sources | <p>See email from New Hampshire DES</p> <p><a href="https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance">https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance</a></p> <p><a href="https://www.newmoa.org/wp-content/uploads/2022/08/NHDES_PFOA_AirModelingDepositionMarch2017.pdf">https://www.newmoa.org/wp-content/uploads/2022/08/NHDES_PFOA_AirModelingDepositionMarch2017.pdf</a></p> <p><a href="https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/env-a-1400.pdf">https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/env-a-1400.pdf</a></p> |

#### 4.9.4. New Jersey DEP

TABLE 39. NEW JERSEY DEP RfC FOR PFOA (CAS 335-67-1)

| Variable                                                                                                       | Value                          | Comment                            |
|----------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------|
| RfC                                                                                                            | 0.007 $\mu\text{g}/\text{m}^3$ | ITSLs are analogous to RfCs        |
| Date                                                                                                           | December 19, 2019              | --                                 |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral toxicity study            | Oral RfD used to calculate an RfC. |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | Loveless, S.E., Finlay, C., Everds, N.E., Frame, S.R., Gillies, P.J., O'Connor, J.C., Powley, C.R., Kennedy, G.L. (2006). Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology 220: 203–217.                                                                                                                   | --                                                                                                                                                                                                                                                                                                                         |
| Species                                                           | Mouse                                                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                                                                                                                                                                                         |
| Target Organ                                                      | Liver                                                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                                                                                                                                                                                         |
| Description of TRV endpoints/ basis for points of departure (POD) | 10% increase in relative liver weight                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                                                                                                                                                                                         |
| Other Endpoints                                                   | --                                                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                                                                                                                                                                                                                                         |
| Uncertainty Factors                                               | Total UF = $10 \times 10 \times 3 = 300$                                                                                                                                                                                                                                                                                                                                                        | UF (sensitive individuals) = 10<br>UF (animal to human) = 3<br>UF (data insufficiency) = 10                                                                                                                                                                                                                                |
| POD Method                                                        | BMDL                                                                                                                                                                                                                                                                                                                                                                                            | Serum level BMDL of 4,350 ng/ml                                                                                                                                                                                                                                                                                            |
| Human Equivalent Concentration in TRV?                            | The target human serum level is: $4350 \text{ ng/mL} / 300 = 14.5 \text{ ng/mL}$                                                                                                                                                                                                                                                                                                                | Where BMDL = 4,350 ng/mL and Combined UF = 300                                                                                                                                                                                                                                                                             |
| Duration of exposure                                              | 14 days                                                                                                                                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                                                                                                                                                         |
| Time Adjustment in TRV?                                           | No                                                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                                                                                                                                                                                                                                         |
| Developmental or Reproductive Effects?                            | Developmental and Reproductive                                                                                                                                                                                                                                                                                                                                                                  | Effects from developmental exposures in mice include full litter resorptions, 10 decreased postnatal survival and growth, delayed development, accelerated sexual maturation in males, persistent liver toxicity (noted above), and delayed mammary gland development. PFOA also causes reproductive toxicity in male mice |
| Oral to inhalation extrapolation                                  | ITSL calculated based on approach in Michigan's <a href="#">R232(1)(b)</a> (see additional notes):<br>ITSL = $\text{RfD} \times (\text{average body weight}) / (\text{inhalation rate per day}) \times \text{unit conversion}$<br>ITSL = $2 \times 10^{-6} \text{ mg/kg/day} \times (70 \text{ kg}) / (20 \text{ m}^3/\text{day}) \times 1000 \mu\text{g/mg}$<br>ISTL = $0.007 \mu\text{g/m}^3$ |                                                                                                                                                                                                                                                                                                                            |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | New Jersey Department of Environmental Protection (NJDEP) toxicologists reviewed the Michigan Department of Environmental Quality's (MDEQ) approach for calculating the ISTL for PFOA. They considered MDEQ's approach alongside alternative approaches, and selected MDEQ's approach as the most conservative (health protective), however they used the NJDEP PFOA RfD of $2 \times 10^{-6}$ mg/kg/day (derived in DWQI, 2017) rather than the USEPA RfD of $2 \times 10^{-5}$ mg/kg/day as used by MDEQ.                                                                                                                                                                                                                                                                         |
| Links to TRV Sources | <a href="https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf">https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf</a><br><br><a href="https://www.nj.gov/dep/watersupply/pdf/pfoa-appendixa.pdf">https://www.nj.gov/dep/watersupply/pdf/pfoa-appendixa.pdf</a> .<br><br><a href="https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level">https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level</a> |

#### 4.9.5. New York DEC

TABLE 40. NEW YORK DEC AGC FOR PFOA (CAS 335-67-1)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                  | Comment                                 |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Annual Guideline Concentration (AGC)                                                                           | 0.0053 $\mu\text{g}/\text{m}^3$                                                                                                                                                                                                                                                        | --                                      |
| Date                                                                                                           | February 12, 2021                                                                                                                                                                                                                                                                      | --                                      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral toxicity study                                                                                                                                                                                                                                                                    | Oral RfD converted to inhalation value. |
| Critical study                                                                                                 | Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L, Fenton SE. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. Toxicol Sci. 2011 Jul;122(1):134-45. doi: 10.1093/toxsci/kfr076. | --                                      |
| Species                                                                                                        | Mouse                                                                                                                                                                                                                                                                                  | --                                      |
| Target Organ                                                                                                   | Liver                                                                                                                                                                                                                                                                                  | --                                      |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Liver toxicity and enlargement                                                                                                                                                                                                                                                         | --                                      |

|                                        |                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                            |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Other Endpoints                        | Hepatocellular adenoma, Leydig cell tumors, and pancreatic acinar cell tumors, delayed mammary gland development                                                                                                                                                        | --                                                                                                                                                                                                                                                         |
| Uncertainty Factors                    | For derivation of RfD: Total UF = $3 \times 3 \times 10 \times 3 \sim 300$                                                                                                                                                                                              | UF (use of LOEL) = 3<br>UF (animal to human) = 3<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 3                                                                                                                                         |
| POD Method                             | LOEL = 0.3 mg/kg-day                                                                                                                                                                                                                                                    | PFOA serum concentration at LOEL was 4.98 mg/L                                                                                                                                                                                                             |
| Human Equivalent Concentration in TRV? | Human equivalent dose ( $HED_{LOEL}$ ) = PFOA serum concentration x PFOA clearance rate<br>= 4.98 mg/L x 0.000092 L/kg-day = 0.00046 mg/kg/day                                                                                                                          | PKAF = estimated PFOA serum clearance (CL) in humans<br>Clearance Level (CL) = Volume of distribution x ( $\ln 2 \div$ human PFOA serum $\frac{1}{2}$ life estimate) = 0.17 L/kg x (0.693 / 1277.5 days) = $9.2 \times 10^{-5}$ L/kg-day (0.092 mL/kg-day) |
| Duration of exposure                   | Daily exposure from GD 1 to GD 17                                                                                                                                                                                                                                       | --                                                                                                                                                                                                                                                         |
| Time Adjustment in TRV?                | No                                                                                                                                                                                                                                                                      | No explicit time adjustment in calculation.                                                                                                                                                                                                                |
| Developmental or Reproductive Effects? | Developmental                                                                                                                                                                                                                                                           | Citing USEPA assessment.                                                                                                                                                                                                                                   |
| Oral to inhalation extrapolation       | RfD = $1.5 \times 10^{-3}$ µg/kg/day [See calculation in Additional Notes]<br>Oral to inhalation extrapolation = 70kg / 20m <sup>3</sup> /day<br><br>RfC = $1.5 \times 10^{-3}$ µg/kg/day * (70 kg) / (20 m <sup>3</sup> /day) = $5.3 \times 10^{-3}$ µg/m <sup>3</sup> |                                                                                                                                                                                                                                                            |
| Additional notes                       | RfD derived using <a href="#">6 NYCRR 702.5</a> :<br><br>RfD = $HED_{LOEL} / UF$<br>RfD = 0.00046 mg/kg/day / 300 = $1.5 \times 10^{-6}$ µg/kg-day<br><br>NYDOH will be reevaluating the AGC for PFOA this year.                                                        |                                                                                                                                                                                                                                                            |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <p>US EPA (U.S. Environmental Protection Agency). 2016. Health Effects Support Document for Perfluorooctanoic Acid (PFOA). Office of Water. EPA 822-R-16-003. Last accessed (03/21/2019) at <a href="https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-healthadvisories-pfoa-and-pfos">https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-healthadvisories-pfoa-and-pfos</a>.</p> <p>Tardiff RG, Carson ML, Sweeney LM, et al. 2009. Derivation of a drinking water equivalent level (DWEL) related to the maximum contaminant level goal for perfluorooctanoic acid (PFOA), a persistent water soluble compound. Food Chem Toxicol. 47:2557-2589.<br/><a href="https://www.sciencedirect.com/science/article/abs/pii/S0278691509003433?via%3Dihub">https://www.sciencedirect.com/science/article/abs/pii/S0278691509003433?via%3Dihub</a>.</p> <p>Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L, Fenton SE. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. Toxicol Sci. 2011 Jul;122(1):134-45.<br/><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143465/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143465/</a>.</p> <p>NEW YORK STATE HUMAN HEALTH FACT SHEET1 Ambient Water Quality Value for Protection of Human Health and Sources of Potable Water SUBSTANCE: Perfluorooctanoic Acid (PFOA).<br/><a href="https://extapps.dec.ny.gov/docs/water_pdf/pfoahumanhealth.pdf">https://extapps.dec.ny.gov/docs/water_pdf/pfoahumanhealth.pdf</a></p> |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.9.6. Texas TCEQ

TABLE 41. TEXAS TCEQ SHORT- AND LONG-TERM ESLS AND RfC FOR PFOA (CAS 335-67-1)

| Variable       | Value                                    | Comment                                                                                                                 |
|----------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Short-Term ESL | 0.05 µg/m <sup>3</sup>                   | No supporting documentation for Short-Term ESL. Short-term ESL set on July 12, 2011. Information below for updated RfC. |
| Long-Term ESL  | 0.005 µg/m <sup>3</sup>                  | No supporting documentation for Long-Term ESL. Long-term ESL set on July 12, 2011. Information below for updated RfC.   |
| RfC            | 4.1 x 10 <sup>-3</sup> µg/m <sup>3</sup> | ***Information for this row and below comes from a February 14, 2023 update to derivation of PFAS RfDs and RfCs.        |
| Date           | February 14, 2023                        | --                                                                                                                      |

|                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Inhalation study                                                                                                                                                                                                                                                                                                                                                | --                                                                                                                                                              |
| Critical study                                                                                                 | Kennedy GL, Hall GT, Brittelli MR, et al. 1986. Inhalation toxicity of ammonium perfluorooctanoate. Food Chem Toxicol 24(12):1325-1329.                                                                                                                                                                                                                         | --                                                                                                                                                              |
| Species                                                                                                        | Rats                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                                                              |
| Target Organ                                                                                                   | Liver                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                              |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Increases in relative and absolute liver weights and histological alternations in the livers                                                                                                                                                                                                                                                                    | --                                                                                                                                                              |
| Other Endpoints                                                                                                | 10% decrease in newborn bodyweight and 37% decreased weight gain in dams                                                                                                                                                                                                                                                                                        | --                                                                                                                                                              |
| Uncertainty Factors                                                                                            | Total UF = $81 \times 3 \times 10 \times 10 \times 10 = 243,000$                                                                                                                                                                                                                                                                                                | UF (animal to human TK) = 81<br>UF (animal to human TD) = 3<br>UF (subacute to chronic) = 10<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 10 |
| POD Method                                                                                                     | NOAEL                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                              |
| Human Equivalent Concentration in TRV?                                                                         | Not explicit in calculation                                                                                                                                                                                                                                                                                                                                     | UF applied                                                                                                                                                      |
| Duration of exposure                                                                                           | Whole-body exposure to APFO dusts 6 hours/day on gestation days 6 to 15                                                                                                                                                                                                                                                                                         | --                                                                                                                                                              |
| Time Adjustment in TRV?                                                                                        | No                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                                                                              |
| Developmental or Reproductive Effects?                                                                         | Developmental                                                                                                                                                                                                                                                                                                                                                   | PFOA oral RfD in same document derived based on developmental endpoints.                                                                                        |
| Oral to inhalation extrapolation                                                                               | No                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                 |
| Additional notes                                                                                               | <p>PFOA RfC = <math>1 \text{ mg/m}^3 / (81 \times 3 \times 10 \times 10 \times 10) = 4.1\text{E-}06 \text{ mg/m}^3 = 0.0041 \text{ }\mu\text{g/m}^3</math></p> <p>No information was available on the ESLs that were set by TCEQ. ERG emailed TCEQ for additional information and was provided the documentation for the updated RfC values described here.</p> |                                                                                                                                                                 |



|                      |                                                                                                                                                                                                                                                                                                                           |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a><br><br>TAMIS database:<br><a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a> |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.9.7. Wisconsin DNR

**TABLE 42. WISCONSIN DNR 24-HOUR AAL FOR AMMONIUM PERFLUOROOCCTANOATE (APFO) (CAS 3825-26-1)**

| Variable                                                                                                       | Value                                                                                                                                                                               | Comment                                     |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| 24-hour AAL                                                                                                    | 0.24 µg/m <sup>3</sup>                                                                                                                                                              | Ammonium perfluorooctanoate, salt of PFOA   |
| Date                                                                                                           | --                                                                                                                                                                                  | Not clear when added to list.               |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit                                                                                                                                                         | ACGIH's TLV and biological indices for 2000 |
| Critical study                                                                                                 | --                                                                                                                                                                                  | --                                          |
| Species                                                                                                        | --                                                                                                                                                                                  | No information on derivation.               |
| Target Organ                                                                                                   | --                                                                                                                                                                                  | No information on derivation.               |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                                                                                                                                                  | No information on derivation.               |
| Other Endpoints                                                                                                | --                                                                                                                                                                                  | No information on derivation.               |
| Uncertainty Factors                                                                                            | --                                                                                                                                                                                  | No information on derivation.               |
| POD Method                                                                                                     | --                                                                                                                                                                                  | No information on derivation.               |
| Human Equivalent Concentration in TRV?                                                                         | --                                                                                                                                                                                  | No information on derivation.               |
| Duration of exposure                                                                                           | --                                                                                                                                                                                  | No information on derivation.               |
| Time Adjustment in TRV?                                                                                        | --                                                                                                                                                                                  | No information on derivation.               |
| Developmental or Reproductive Effects?                                                                         | -                                                                                                                                                                                   |                                             |
| Oral to inhalation extrapolation                                                                               | -                                                                                                                                                                                   |                                             |
| Additional notes                                                                                               | Wisconsin DNR provided information on derivation. 24-hour averaging time ambient air standard set as 2.4% of the ACGIH 2000 TLV.<br><br>ACGIH 2000 TLV documentation not available. |                                             |

|                      |                                                                                                                                                                                                                                                                                                                                       |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <p>See Email and documents from Wisconsin DNR</p> <p><a href="http://docs.legis.wisconsin.gov/code/admin_code/nr/400/445.pdf">http://docs.legis.wisconsin.gov/code/admin_code/nr/400/445.pdf</a></p> <p><a href="https://dnr.wisconsin.gov/topic/AirQuality/Rules.html">https://dnr.wisconsin.gov/topic/AirQuality/Rules.html</a></p> |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.10. Perfluorooctane sulfonic acid (PFOS) (CAS 1763-23-1)

ERG identified both carcinogenic and non-carcinogenic health-based screening values for PFOS. The identified values come from four different state agencies and range from 0.006 to 0.1 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental and reproductive effects were observed for PFOS in various TRV source documents. In addition, [ATSDR's 2022 Toxicological Profile](#) found multiple epidemiological studies with developmental or reproductive effects including associations with effects on reproductive hormone levels, sperm, menopause onset, endometriosis, breastfeeding duration, fertility, pregnancy outcomes, birth outcomes, neurodevelopmental outcomes, and development of the reproductive system. The Toxicological Profile also cites developmental or reproductive effects for numerous laboratory animal studies.

PFOS is not present on the DOT list of inhalation hazards.

**TABLE 43. INHALATION TRVs FOR PFOS (CAS 1763-23-1)**

| State/Agency   | TRV            | TRV                      | Classification          | DEQ Notes                                                        |
|----------------|----------------|--------------------------|-------------------------|------------------------------------------------------------------|
| Michigan EGLE  | 24-Hour ISTL   | 0.0004 µg/m <sup>3</sup> | Non-cancer, acute       | Unmodified but proposed for use as chronic rather than acute TRV |
| Minnesota DH   | RAA            | 0.011 µg/m <sup>3</sup>  | Non-cancer, acute       | Unmodified                                                       |
|                | RAA            | 0.011 µg/m <sup>3</sup>  | Non-cancer, sub-chronic | Not needed because same as acute                                 |
|                | RAA            | 0.011 µg/m <sup>3</sup>  | Non-cancer, chronic     | Not needed because same as acute                                 |
| New Jersey DEP | RfC            | 0.006 µg/m <sup>3</sup>  | Non-cancer, chronic     | Based on older tox study than Michigan                           |
| Texas TCEQ     | Short-term ESL | 0.1 µg/m <sup>3</sup>    | Non-cancer, acute       | No derivation information available                              |
|                | Long-term ESL  | 0.01 µg/m <sup>3</sup>   | Non-cancer, chronic     | No derivation information available                              |

|  |     |                         |                     |                                        |
|--|-----|-------------------------|---------------------|----------------------------------------|
|  | RfC | 0.081 µg/m <sup>3</sup> | Non-cancer, chronic | Based on older tox study than Michigan |
|--|-----|-------------------------|---------------------|----------------------------------------|

The Michigan value is based on an oral RfD derived by EPA that is chronic, and Michigan did not make any quantitative adjustments to the value to make it an acute value. It is chosen over other options because it is based on the very newest EPA oral RfD (March 2024) and very recent studies in humans.

#### 4.10.1. Michigan EGLE

TABLE 44. MICHIGAN EGLE ITSL FOR PFOS (CAS 1763-23-1)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Comment                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| ITSL                                                                                                           | 0.0004 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 24-hour time averaging                                                                                                                             |
| Date                                                                                                           | April 25, 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Original set in February 16, 2018 then updated on April 25, 2024 after EPA updated its final Human Health Toxicity Assessment for PFOS.            |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Derived from 2024 EPA RfD for PFOS of 1E-7 mg/kg/day,.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | --                                                                                                                                                 |
| Critical study                                                                                                 | <p>Wikström, S; Hussein, G; Lingroth Karlsson, A; Lindh, CH; Bornehag, CG. (2021). Exposure to perfluoroalkyl substances in early pregnancy and risk of sporadic first trimester miscarriage. Scientific Reports 11: 3568.<br/> <a href="http://dx.doi.org/10.1038/s41598-021-82748-6">http://dx.doi.org/10.1038/s41598-021-82748-6</a></p> <p>Dong, Z; Wang, H; Yu, YY; Li, YB; Naidu, R; Liu, Y. (2019). Using 2003-2014 U.S. NHANES data to determine the associations between per- and polyfluoroalkyl substances and cholesterol: Trend and implications. Ecotoxicology and Environmental Safety 173: 461- 468.</p> | EPA RfD based on epidemiologic studies that showed developmental (decreased birth weight) and cardiovascular (increased total cholesterol) effects |

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                            |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Species                                                           | Human                                                                                                                                                                                                                                                                                                                                                                                                                        | Epidemiological studies.                                                                                                   |
| Target Organ                                                      | Cardiovascular, developmental                                                                                                                                                                                                                                                                                                                                                                                                | --                                                                                                                         |
| Description of TRV endpoints/ basis for points of departure (POD) | Developmental (decreased birth weight) and cardiovascular (increased total cholesterol)                                                                                                                                                                                                                                                                                                                                      | --                                                                                                                         |
| Other Endpoints                                                   | Many other effects in toxicity assessment.                                                                                                                                                                                                                                                                                                                                                                                   | --                                                                                                                         |
| Uncertainty Factors                                               | EGLE did not apply UFs to TRV calculation.                                                                                                                                                                                                                                                                                                                                                                                   | EPA applied uncertainty factors when deriving the oral RfD, but EGLE did not apply uncertainty factors in its calculation. |
| POD Method                                                        | EGLE used an oral RfD to RfC conversion                                                                                                                                                                                                                                                                                                                                                                                      | EPA used benchmark dose modeling (BMDL) to derive multiple oral RfDs                                                       |
| Human Equivalent Concentration in TRV?                            | Yes in EPA oral RfD derivation.                                                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                                         |
| Duration of exposure                                              | Various                                                                                                                                                                                                                                                                                                                                                                                                                      | --                                                                                                                         |
| Time Adjustment in TRV?                                           | No (see note)                                                                                                                                                                                                                                                                                                                                                                                                                | ITSL is determined for a 24-hour time averaging; however, no explicit time-adjustment is present in the TRV derivation.    |
| Developmental or Reproductive Effects?                            | Developmental and Reproductive in PFOS Toxicity Assessment                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                            |
| Oral to inhalation extrapolation                                  | $ITSL = RfD \times (\text{Default Body weight}) / (\text{Default Inhalation rate}) \times \text{unit conversion}$<br>$ITSL = 1E-7 \text{ mg/kg/day} \times 70\text{kg}/20\text{m}^3 \times 1000 \text{ }\mu\text{g/mg}$<br>$ITSL = 0.00035 \text{ }\mu\text{g/m}^3$ , rounded to 1 significant figure as $0.0004 \text{ }\mu\text{g/m}^3$                                                                                    |                                                                                                                            |
| Additional notes                                                  | --                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                            |
| Links to TRV Sources                                              | <a href="https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=335671&amp;cmdSubmit=Submit">https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=335671&amp;cmdSubmit=Submit</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/1763-23-1/1763-23-1_24hr_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/1763-23-1/1763-23-1_24hr_ITSL.pdf</a> |                                                                                                                            |

#### 4.10.2. Minnesota DH

TABLE 45. MINNESOTA DH RAA VALUE FOR PFOS (CAS 1763-23-1)

| Variable                                | Value                           | Comment                                                                                                                                                                  |
|-----------------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-Cancer Risk Assessment Advice (RAA) | $0.011 \text{ }\mu\text{g/m}^3$ | Short-term (>24 hours; < 30 days), sub-chronic (>30days and <10% of lifetime), and chronic (>10% of lifetime) all have the same value of $0.011 \text{ }\mu\text{g/m}^3$ |
| Date                                    | June 2021                       | --                                                                                                                                                                       |

|                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral mouse study                                                                                                                                                                                                                                                                                                                                                                                                                                                 | --                                                                                                                                                                        |
| Critical study                                                                                                 | Dong, G. H., Liu, M. M., Wang, D., Zheng, L., Liang, Z. F., & Jin, Y. H. (2011). Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. Archives of toxicology, 85, 1235-1244.                                                                                                                                                                                                                 | --                                                                                                                                                                        |
| Species                                                                                                        | Mouse                                                                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                                                                        |
| Target Organ                                                                                                   | Immune system                                                                                                                                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                                                                        |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Increased IL-4 and decreased SRBC specific IgM levels                                                                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                                                                        |
| Other Endpoints                                                                                                | Decreased pup body weight; increased fasting serum insulin and glucose in pups; suppressed SRBC response, increased NK cell activity and decreased IgM; decreased total and free T4 (maternal and pups); decreased adrenal weight, decreased serum corticosterone and adrenocorticotrophic hormone levels in serum, and corticotropin-releasing hormone concentration in hypothalamus; and changes in cholesterol and histological changes in the liver (adults) | --                                                                                                                                                                        |
| Uncertainty Factors                                                                                            | Total UF = 100                                                                                                                                                                                                                                                                                                                                                                                                                                                   | UF (animal to human) = 3<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 3                                                                                |
| POD Method                                                                                                     | NOAEL                                                                                                                                                                                                                                                                                                                                                                                                                                                            | NOAEL of 2.36 µg/mL                                                                                                                                                       |
| Human Equivalent Concentration in TRV?                                                                         | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                              | HED = POD x DAF = 2.36 mg/L x 0.00013 L/kg-d = 0.000307mg/kg-d<br><i>Where DAF is dose adjustment factor</i><br><br>RfD = HED/Total UF = 0.000307/100 = 0.0000031 mg/kg-d |
| Duration of exposure                                                                                           | 60 days                                                                                                                                                                                                                                                                                                                                                                                                                                                          | --                                                                                                                                                                        |

|                                        |                                                                                                                                                                                                                                                                                                                                                  |    |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Time Adjustment in TRV?                | Yes                                                                                                                                                                                                                                                                                                                                              | -- |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                               | -- |
| Oral to inhalation extrapolation       | <p>RfD = 0.0000031 (mg/kg/day)</p> <p>RAA = RfD * oral-inhalation scaling factor * unit conversion</p> <p>RAA = 0.0000031 (mg/kg/day) x (70 kg/20 m<sup>3</sup>/day) x (1000 µg/mg) = 0.0108 rounded to 0.011 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |    |
| Additional notes                       | --                                                                                                                                                                                                                                                                                                                                               |    |
| Links to TRV Sources                   | <p><a href="https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfos.pdf">https://www.health.state.mn.us/communities/environment/risk/docs/guidance/air/pfos.pdf</a></p> <p><a href="https://pubmed.ncbi.nlm.nih.gov/21327619/">https://pubmed.ncbi.nlm.nih.gov/21327619/</a></p>                                      |    |

### 4.10.3. New Jersey DEP

TABLE 46. NEW JERSEY RfC FOR PFOS (CAS 1763-23-1)

| Variable                                                                                                       | Value                                                                                                                                                                               | Comment                                                     |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| RfC                                                                                                            | 0.006 µg/m <sup>3</sup>                                                                                                                                                             | ITSLs are analogous to RfCs                                 |
| Date                                                                                                           | June 5, 2018                                                                                                                                                                        | --                                                          |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral toxicity study                                                                                                                                                                 | Oral RfD used to calculate an RfC.                          |
| Critical study                                                                                                 | Dong GH, Zhang YH, Zheng L, Liu W, Jin YH, He QC. 2009. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. Arch Toxicol. 83:805-815 | --                                                          |
| Species                                                                                                        | Mouse                                                                                                                                                                               | --                                                          |
| Target Organ                                                                                                   | Immune system                                                                                                                                                                       | --                                                          |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Decreased plaque forming cell response                                                                                                                                              | --                                                          |
| Other Endpoints                                                                                                | --                                                                                                                                                                                  | --                                                          |
| Uncertainty Factors                                                                                            | Total UF = 10 x 3 = 30                                                                                                                                                              | UF (sensitive individuals) = 10<br>UF (animal to human) = 3 |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                      |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| POD Method                             | NOAEL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Where NOAEL = 674 ng/mL and                                                                                          |
| Human Equivalent Concentration in TRV? | The target human serum level is:<br>POD / UF<br>$674 \text{ ng/mL} / 30 = 22.5 \text{ ng/mL}$ where<br>$674 \text{ ng/mL}$ is the Animal $\text{POD}_{\text{serum}}$<br><br>$\text{RfD} = 22.5 \text{ ng/mL} / 8.1 \times 10^{-5}$<br>$\text{L/kg/day} = 1.8 \times 10^{-6} \text{ mg/kg/day}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Combined UF = 30<br><br>Human clearance factor of $8.1 \times 10^{-5}$<br>$\text{L/kg/day}$ obtained from USEPA 2016 |
| Duration of exposure                   | 60 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | --                                                                                                                   |
| Time Adjustment in TRV?                | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                   |
| Developmental or Reproductive Effects? | Various developmental and reproductive effects.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                      |
| Oral to inhalation extrapolation       | ITSL calculated based on approach in Michigan's <a href="#">R232(1)(b)</a> (see additional notes):<br>$\text{ITSL} = \text{RfD} * (\text{average body weight}) / (\text{inhalation rate per day}) * \text{unit conversion}$<br>$\text{ITSL} = 1.8 \times 10^{-6} \text{ mg/kg/day} * (70 \text{ kg}) / (20 \text{ m}^3/\text{day}) * 1000 \mu\text{g/mg}$<br>$\text{ITSL} = 0.006 \mu\text{g/m}^3$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                      |
| Additional notes                       | New Jersey Department of Environmental Protection (NJDEP) toxicologists reviewed the Michigan Department of Environmental Quality's (MDEQ) approach for calculating the ISTL for PFOS. They considered MDEQ's approach alongside alternative approaches, and selected MDEQ's approach as the most conservative (health protective), however they used the NJDEP PFOS RfD of $1.8 \times 10^{-6} \text{ mg/kg/day}$ (derived in DWQI, 2018) rather than the USEPA RfD of $2 \times 10^{-5} \text{ mg/kg/day}$ as used by MDEQ.                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                      |
| Links to TRV Sources                   | <a href="https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf">https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf</a><br><br>DWQI. 2018. New Jersey Water Quality Institute. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). <a href="https://www.nj.gov/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf">https://www.nj.gov/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf</a><br><br><a href="https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level">https://casetext.com/regulation/michigan-administrative-code/departments-environmental-quality/air-quality-division/part-2-air-use-approval/section-r-3361232-methodology-for-determining-initial-threshold-screening-level</a> |                                                                                                                      |

#### 4.10.4. Texas TCEQ

TABLE 47. TEXAS TCEQ SHORT- AND LONG-TERM ESL AND RFC FOR PFOS (CAS 1763-23-1)

| Variable | Value | Comment |
|----------|-------|---------|
|----------|-------|---------|

|                                                                                                                |                                                                                                                                                                                                  |                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Short-term ESL                                                                                                 | 0.1 µg/m <sup>3</sup>                                                                                                                                                                            | No supporting documentation for Short-Term ESL. Short-term ESL set on July 12, 2011. Information below for updated RfC. |
| Long-term ESL                                                                                                  | 0.01 µg/m <sup>3</sup>                                                                                                                                                                           | No supporting documentation for Long-Term ESL. Long-term ESL set on July 12, 2011. Information below for updated RfC.   |
| RfC                                                                                                            | 0.081 µg/m <sup>3</sup>                                                                                                                                                                          | ***Information for this row and below comes from a February 14, 2023 update to derivation of PFAS RfDs and RfCs.        |
| Date                                                                                                           | February 14, 2023                                                                                                                                                                                | --                                                                                                                      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                                                                                                                                                                                   | --                                                                                                                      |
| Critical study                                                                                                 | Zeng HC, Li YY, Zhang L, et al. 2011. Prenatal exposure to perfluorooctanesulfonate in rat resulted in long-lasting changes of expression of synapsins and synaptophysin. Synapse 65(3): 225-33. | --                                                                                                                      |
| Species                                                                                                        | Rats                                                                                                                                                                                             | --                                                                                                                      |
| Target Organ                                                                                                   | Brain (developmental neurotoxicity)                                                                                                                                                              | --                                                                                                                      |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Adverse development of three structures of synapses in the hippocampus: active zone length, number of vesicles per area, and synaptic interface curvature                                        | Maternal and offspring.                                                                                                 |
| Other Endpoints                                                                                                | --                                                                                                                                                                                               | --                                                                                                                      |
| Uncertainty Factors                                                                                            | For deriving the RfD: Total UF = 263 x 1 x 10 x 10 x 1 = 26,300                                                                                                                                  | Interspecies TK UF = 263<br>Interspecies TD UF = 1<br>LOAEL to NOAEL UF = 10<br>Intrahuman UF = 10<br>Database UF = 1   |
| POD Method                                                                                                     | LOAEL                                                                                                                                                                                            | LOAEL of 0.6 mg/kg/day for adverse effects to the hippocampus synaptic structures                                       |
| Human Equivalent Concentration in TRV?                                                                         | Not explicit in calculation                                                                                                                                                                      | UFs applied.                                                                                                            |
| Duration of exposure                                                                                           | Gestation days 0 to 20                                                                                                                                                                           | --                                                                                                                      |
| Time Adjustment in TRV?                                                                                        | No                                                                                                                                                                                               | --                                                                                                                      |



|                                        |                                                                                                                                                                                                                                                                                                                                                             |                                       |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Developmental or Reproductive Effects? | Developmental                                                                                                                                                                                                                                                                                                                                               | Critical effect is neurodevelopmental |
| Oral to inhalation extrapolation       | <p>PFOS RfD = 0.6 mg/kg/day / (263 x 1 x 10 x 10 x 1) = 2.3E-05 mg/kg/day</p> <p>Using PFOS RfD = 2.3E-05 mg/kg/day:<br/> PFOS RfC = 2.3E-05 mg/kg/day x 70 kg / 20 m<sup>3</sup>/day = 8.1E-05 mg/m<sup>3</sup> = 0.081 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |                                       |
| Additional notes                       | --                                                                                                                                                                                                                                                                                                                                                          |                                       |
| Links to TRV Sources                   | <a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a><br><br>TAMIS database:<br><a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a>                                   |                                       |

#### 4.11. Perfluorooctanesulfonamide (PFOSA) (CAS 754-91-6)

ERG identified a non-carcinogenic health-based RfC for PFOSA. The identified value comes from Texas (TCEQ), which uses PFOA as a surrogate for PFOSA.<sup>1</sup> Cancer screening values were not identified.

Developmental and reproductive effects were observed for PFOA in the source document but not PFOSA. In addition, [ATSDR's 2022 Toxicological Profile](#) cited a study that found an increased time to pregnancy associated with serum FOSA levels (though the author noted that the results should be interpreted with caution), birth weight in boys, and neurodevelopmental outcomes.

PFOSA is not present on the DOT list of inhalation hazards.

Did not use the TCEQ value but did apply the TCEQ rationale (highlighted in footnote) that PFOA can be used as a 1:1 surrogate for this TAC. Therefore, DEQ proposes to apply the DEQ-proposed TRVs and target organ information for PFOA to this TAC as well.

##### 4.11.1. Texas TCEQ

TABLE 48. TEXAS TCEQ RfC FOR PFOSA (CAS 754-91-6)

| Variable | Value                                    | Comment                                                                                                |
|----------|------------------------------------------|--------------------------------------------------------------------------------------------------------|
| RfC      | 4.1 x 10 <sup>-3</sup> µg/m <sup>3</sup> | ***TCEQ uses PFOA as a surrogate. Information in this table is for PFOA RfC derivation (see footnote). |

<sup>1</sup> TCEQ's justification for using PFOA as a surrogate for PFOSA is as follows: "For perfluorooctane sulfonamide (PFOSA), only LD50 data were found in the Registry of Toxic Effects of Chemical Substances (RTECS). The rodent oral LD50 of > 172 mg/kg for PFOSA may be similar to that for PFOA (LD50 of 189 mg/kg), another 8-carbon PFAS for which the toxicity database is more robust. The RfD for PFOA has a more scientifically defensible basis than using an uncertain LD50 value to derive an RfD for PFOSA. The RfD for PFOA was used as the surrogate for PFOSA."

|                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date                                                                                                           | February 14, 2023                                                                                                                                                                                                                                                                                                                                               | --                                                                                                                                                              |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Inhalation study                                                                                                                                                                                                                                                                                                                                                | --                                                                                                                                                              |
| Critical study                                                                                                 | Kennedy GL, Hall GT, Brittelli MR, et al. 1986. Inhalation toxicity of ammonium perfluorooctanoate. Food Chem Toxicol 24(12):1325-1329.                                                                                                                                                                                                                         | --                                                                                                                                                              |
| Species                                                                                                        | Rats                                                                                                                                                                                                                                                                                                                                                            | --                                                                                                                                                              |
| Target Organ                                                                                                   | Liver                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                              |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Increases in relative and absolute liver weights and histological alternations in the livers                                                                                                                                                                                                                                                                    | --                                                                                                                                                              |
| Other Endpoints                                                                                                | 10% decrease in newborn bodyweight and 37% decreased weight gain in dams                                                                                                                                                                                                                                                                                        | --                                                                                                                                                              |
| Uncertainty Factors                                                                                            | Total UF = $81 \times 3 \times 10 \times 10 \times 10 = 243,000$                                                                                                                                                                                                                                                                                                | UF (animal to human TK) = 81<br>UF (animal to human TD) = 3<br>UF (subacute to chronic) = 10<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 10 |
| POD Method                                                                                                     | NOAEL                                                                                                                                                                                                                                                                                                                                                           | --                                                                                                                                                              |
| Human Equivalent Concentration in TRV?                                                                         | Not explicit in calculation                                                                                                                                                                                                                                                                                                                                     | UF applied                                                                                                                                                      |
| Duration of exposure                                                                                           | Whole-body exposure to APFO dusts 6 hours/day on gestation days 6 to 15                                                                                                                                                                                                                                                                                         | --                                                                                                                                                              |
| Time Adjustment in TRV?                                                                                        | No                                                                                                                                                                                                                                                                                                                                                              | --                                                                                                                                                              |
| Developmental or Reproductive Effects?                                                                         | Developmental                                                                                                                                                                                                                                                                                                                                                   | PFOA oral RfD in same document derived based on developmental endpoints.                                                                                        |
| Oral to inhalation extrapolation                                                                               | No                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                 |
| Additional notes                                                                                               | <p>PFOA RfC = <math>1 \text{ mg/m}^3 / (81 \times 3 \times 10 \times 10 \times 10) = 4.1\text{E-}06 \text{ mg/m}^3 = 0.0041 \text{ }\mu\text{g/m}^3</math></p> <p>No information was available on the ESLs that were set by TCEQ. ERG emailed TCEQ for additional information and was provided the documentation for the updated RfC values described here.</p> |                                                                                                                                                                 |

|                      |                                                                                                                                                                            |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a>                                    |
|                      | TAMIS database:<br><a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a> |

#### 4.12. Perfluorononanoic acid (PFNA) (CAS 375-95-1)

ERG identified a non-carcinogenic health-based RfC for PFNA. The identified value comes from Texas (TCEQ). Cancer screening values were not identified.

Developmental or reproductive effects were not observed for PFNA the TCEQ TRV source document. However, [ATSDR's 2022 Toxicological Profile](#) found multiple epidemiological studies with developmental or reproductive effects including associations with effects on reproductive hormone levels, menopause onset, breastfeeding duration, and fertility, pregnancy outcomes, birth outcomes, neurodevelopmental outcomes, and development of the reproductive system. The Toxicological Profile also cites developmental or reproductive effects for multiple laboratory animal studies.

PFNA is not present on the DOT list of inhalation hazards.

This TCEQ RfC is the only value available. DEQ proposes to modify and apply it as an acute rather than a chronic TRV. The exposure was only 4 hours long, and that leaves too much uncertainty to use it for a chronic value as TCEQ has done. DEQ also proposes to adjust exposure time from 4 to 24 hours. See [Document 4: Proposed TRVs Where DEQ is the Authoritative Source](#) for details on these modifications. No other values available to choose from for inhalation. One strength of the study upon which this value is based is that it was an inhalation toxicity study, so no route-to-route extrapolation was necessary.

##### 4.12.1. Texas TCEQ

TABLE 49. TEXAS TCEQ RfC FOR PFNA (CAS 375-95-1)

| Variable                                                                                                       | Value                      | Comment |
|----------------------------------------------------------------------------------------------------------------|----------------------------|---------|
| RfC                                                                                                            | 0.028 µg/m <sup>3</sup>    | --      |
| Date                                                                                                           | February 14, 2023          | --      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Acute inhalation rat study | --      |

|                                                                   |                                                                                                                                                                            |                                                                                                                                                 |
|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | Kinney LA, Chromey NC, Kennedy Jr GL. 1989. Acute inhalation toxicity of ammonium perfluorononanoate. Food Chem Toxicol 21(1):46-68.                                       | --                                                                                                                                              |
| Species                                                           | Rats                                                                                                                                                                       | --                                                                                                                                              |
| Target Organ                                                      | Lungs                                                                                                                                                                      | --                                                                                                                                              |
| Description of TRV endpoints/ basis for points of departure (POD) | Lung noise and labored breathing                                                                                                                                           | --                                                                                                                                              |
| Other Endpoints                                                   | 18% reduced body weight five-days post exposure                                                                                                                            | --                                                                                                                                              |
| Uncertainty Factors                                               | Total UF = $81 \times 3 \times 10 \times 10 \times 10 = 243,000$                                                                                                           | Interspecies TK UF = 81<br>Interspecies TD UF = 3<br>Subacute to chronic UF = 10<br>Intrahuman UF = 10<br>Database UF (data insufficiency) = 10 |
| POD Method                                                        | NOAEL                                                                                                                                                                      | NOAEL of 67 mg/m <sup>3</sup>                                                                                                                   |
| Human Equivalent Concentration in TRV?                            | Not explicit in calculation                                                                                                                                                | UF applied.                                                                                                                                     |
| Duration of exposure                                              | 4 hours                                                                                                                                                                    |                                                                                                                                                 |
| Time Adjustment in TRV?                                           | No                                                                                                                                                                         |                                                                                                                                                 |
| Developmental or Reproductive Effects?                            | No                                                                                                                                                                         |                                                                                                                                                 |
| Oral to inhalation extrapolation                                  | No                                                                                                                                                                         |                                                                                                                                                 |
| Additional notes                                                  | PFNA RfC = 67 mg/m <sup>3</sup> / ( $81 \times 3 \times 10 \times 10 \times 10$ ) = 2.8E-05 mg/m <sup>3</sup> = 0.028 µg/m <sup>3</sup>                                    |                                                                                                                                                 |
| Links to TRV Sources                                              | TAMIS database:<br><a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a> |                                                                                                                                                 |
|                                                                   |                                                                                                                                                                            |                                                                                                                                                 |

#### 4.13. Perfluorodecanoic acid (PFDA) (CAS 335-76-2)

ERG identified a non-carcinogenic RfC for PFDA. The identified value comes from Texas (TCEQ). Cancer screening values were not identified.

Developmental or reproductive effects were not observed for PFDA the TCEQ TRV source document. However, [ATSDR's 2022 Toxicological Profile](#) found multiple epidemiological studies with developmental or reproductive effects including associations with effects on reproductive hormone levels, sperm, breastfeeding duration, pregnancy outcomes, birth outcomes, neurodevelopmental outcomes, and development of the reproductive system. The Toxicological Profile also cites developmental or reproductive effects for multiple laboratory animal studies.

PFDA is not present on the DOT list of inhalation hazards.

DEQ proposes to adopt this TCEQ value without modification as the chronic TRV for this TAC. There were no other options available from sources researched by ERG.

#### 4.13.1. Texas TCEQ

TABLE 50. TEXAS TCEQ RfD FOR PERFLUORODECANOIC ACID (PFDA) (CAS 335-76-2)

| Variable                                                                                                       | Value                                                                                                                                                                                                   | Comment                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| RfC                                                                                                            | 0.053 $\mu\text{g}/\text{m}^3$                                                                                                                                                                          | --                                                                                                                                                              |
| Date                                                                                                           | February 14, 2023                                                                                                                                                                                       | --                                                                                                                                                              |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral rat study                                                                                                                                                                                          | RfC derived from oral RfD                                                                                                                                       |
| Critical study                                                                                                 | Kawashima Y, Kobayashi H, Miura H, et al. 1995. Characterization of hepatic responses of rat to administration of perfluorooctanoic and perfluorodecanoic acids at low levels. Toxicology 99(3):169178. | TCEQ references USEPA 2022 tox assessment, which cites Kawashima et al. 1995                                                                                    |
| Species                                                                                                        | Rat                                                                                                                                                                                                     | --                                                                                                                                                              |
| Target Organ                                                                                                   | Liver                                                                                                                                                                                                   | --                                                                                                                                                              |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Increased liver weight                                                                                                                                                                                  | --                                                                                                                                                              |
| Other Endpoints                                                                                                | Body weight gain reduction, food consumption reduction                                                                                                                                                  | --                                                                                                                                                              |
| Uncertainty Factors                                                                                            | For calculating RfD:<br>Total UF = $81 \times 1 \times 10 \times 10 \times 10 = 81,000$                                                                                                                 | UF (animal to human TK) = 81<br>UF (animal to human TD) = 1<br>UF (subacute to chronic) = 10<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 10 |
| POD Method                                                                                                     | NOAEL                                                                                                                                                                                                   | The LOAEL for increased liver weight ( $\approx 30\%$ greater than control) was 2.4 mg/kg/day, with an associated NOAEL of 1.2 mg/kg/day                        |

|                                        |                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | Interspecies UF of 81                                                                                                                                                                                                                                                                                                                                      | “TCEQ will use the most conservative data-based TK interspecies extrapolation factor available from other RfD derivations for longer carbon chain PFAS as a surrogate for PFDA (i.e., the TK interspecies extrapolation factor of 81 for PFOA [8- carbon] is the most conservative surrogate value for PFDA [10- carbon]). TCEQ will assume the ratio of human-to-rodent half-lives for PFDA is the same as that for PFOA (i.e., the PFDA half-lives for both humans and rats/mice are assumed to be increased by the same factor over those for PFOA, maintaining the human-to-rat half-life ratio of approximately 81)” |
| Duration of exposure                   | 1 week (sub-acute)                                                                                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Time Adjustment in TRV?                | Not explicit in calculation                                                                                                                                                                                                                                                                                                                                | Subacute to chronic UF applied.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Oral to inhalation extrapolation       | Yes (see below)                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Additional notes                       | <p>PFDA RfD = 1.2 mg/kg/day / (81 x 1 x 10 x 10 x 10) = 1.5E-05 mg/kg/day</p> <p>Using PDFA RfD = 1.5E-05 mg/kg/day</p> <p>PFDA RfC = 1.5E-05 mg/kg/day x 70 kg/20 m<sup>3</sup>/day = 5.3E-05 mg/m<sup>3</sup> = 0.053 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Links to TRV Sources                   | <p><a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a></p> <p>TAMIS database:<br/><a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a></p>                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

#### 4.14. Perfluorododecanoic acid (PFDoDA) (CAS 307-55-1)

ERG identified a non-carcinogenic health-based screening value for PFDoDA. The identified value comes from Texas. Cancer screening values were not identified.

Developmental or reproductive effects were not observed for PFDoDA the TCEQ TRV source document. However, [ATSDR’s 2022 Toxicological Profile](#) found multiple epidemiological studies with developmental or reproductive effects including associations with effects on reproductive hormone levels and birth

outcomes. The Toxicological Profile also cites developmental or reproductive effects for multiple laboratory animal studies.

PFDoDA is not present on the DOT list of inhalation hazards.

DEQ proposes to adopt this TCEQ value unmodified as chronic TRV for this TAC. No other options are available.

#### 4.14.1. Texas TCEQ

TABLE 51. TEXAS RfC FOR PERFLUORODODECANOIC ACID (PFDoDA) (CAS 307-55-1)

| Variable                                                                                                       | Value                                                                                                                                                                                           | Comment                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| RfC                                                                                                            | 0.042 µg/m <sup>3</sup>                                                                                                                                                                         | *Note TCEQ abbreviates this as PFDoA                                                                                             |
| Date                                                                                                           | February 14, 2023                                                                                                                                                                               | --                                                                                                                               |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Subacute oral rat study                                                                                                                                                                         | --                                                                                                                               |
| Critical study                                                                                                 | Shi Z, Zhang H, Liu Y, et al. 2007. Alterations in gene expression and testosterone synthesis in the testes of male rats exposed to perfluorododecanoic acid. <i>Toxicol Sci</i> 98(1):206-215. | TCEQ references ATSDR 2009 tox profile, which cites Shi et al. 2007                                                              |
| Species                                                                                                        | Rat                                                                                                                                                                                             | --                                                                                                                               |
| Target Organ                                                                                                   | Body weight                                                                                                                                                                                     | --                                                                                                                               |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | 25% reduction in body weight                                                                                                                                                                    | --                                                                                                                               |
| Other Endpoints                                                                                                | Decreased serum testosterone and estradiol                                                                                                                                                      | --                                                                                                                               |
| Uncertainty Factors                                                                                            | For calculating RfD:<br>Total UF = 81 x 10 x 10 x 10 = 81,000                                                                                                                                   | UF (animal to human TK) = 81<br>UF (subacute to chronic) = 10<br>UF (sensitive individuals) = 10<br>UF (data insufficiency) = 10 |
| POD Method                                                                                                     | NOAEL                                                                                                                                                                                           | NOAEL of 1 mg/kg/day for reduced body weight                                                                                     |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | Interspecies UF of 81                                                                                                                                                                                                                                                                                                                                                                         | “TCEQ will use the most conservative data-based TK interspecies extrapolation factor available from other RfD derivations for longer carbon chain PFAS as a surrogate for PFD <sub>o</sub> A (i.e., the TK interspecies extrapolation factor of 81 for PFOA [8-carbon] is the most conservative surrogate value for PFD <sub>o</sub> A [12-carbon]). TCEQ will assume the ratio of human-to-rat half-lives for PFD <sub>o</sub> A is the same as that for PFOA (i.e., the PFD <sub>o</sub> A half-lives for both humans and rats are assumed to be increased by the same factor over those for PFOA, maintaining the human-to-rat half-life ratio of approximately 81).” |
| Duration of exposure                   | 14 day daily oral gavage                                                                                                                                                                                                                                                                                                                                                                      | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Time Adjustment in TRV?                | Not explicit in calculation.                                                                                                                                                                                                                                                                                                                                                                  | Subacute to chronic UF applied.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Oral to inhalation extrapolation       | Yes (see below)                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Additional notes                       | <p>PFD<sub>o</sub>A RfD = 1 mg/kg/day / (81 x 1 x 10 x 10 x 10) = 1.2E-05 mg/kg/day</p> <p>Using PFD<sub>o</sub>A RfD = 1.2E-05 mg/kg/day:<br/> PFD<sub>o</sub>A RfC = 1.2E-05 mg/kg/day x 70 kg / 20 m<sup>3</sup>/day = 4.2E-05 mg/m<sup>3</sup> = 0.042 µg/m<sup>3</sup></p> <p>Where the human adult body weight is 70 kg, and the human daily ventilation volume is 20 m<sup>3</sup></p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Links to TRV Sources                   | <p><a href="https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf">https://www.tceq.texas.gov/downloads/toxicology/pfc/pfcs.pdf</a></p> <p>TAMIS database:<br/> <a href="https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome">https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome</a></p>                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

#### 4.15. 6:2-Fluorotelomersulfonic acid (6:2 FTS) (CAS 27619-97-2)

ERG identified non-carcinogenic health-based screening values for 6:2 FTS. The identified values come from Michigan and ECHA and range from 1 to 1,080 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental and reproductive effects were not observed for 6:2 FTS.

6:2 FTS is not present on the DOT list of inhalation hazards.



TABLE 52. INHALATION TRVs FOR 6:2 FTS (CAS 27619-97-2)

| State/Agency  | TRV               | TRV                                                  | Classification        | DEQ Notes                                          |
|---------------|-------------------|------------------------------------------------------|-----------------------|----------------------------------------------------|
| Michigan EGLE | Annual ISTL       | 1 µg/m <sup>3</sup>                                  | Non-cancer, long-term | Unmodified – no other appropriate values available |
| ECHA          | Occupational DNEL | 1,080 µg/m <sup>3</sup><br>(1.08 mg/m <sup>3</sup> ) | Non-cancer, long-term | Derived based on and for occupational exposures    |

#### 4.15.1. Michigan EGLE

TABLE 53. MICHIGAN EGLE ITSL FOR 6:2 FTS (CAS 27619-97-2)

| Variable                                                                                                       | Value                                                                          | Comment                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ITSL                                                                                                           | 1 µg/m <sup>3</sup>                                                            | Annual Averaging time                                                                                                                                                   |
| Date                                                                                                           | September 24, 2020                                                             | --                                                                                                                                                                      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | RfD derived from 90-day (subchronic) oral rat study conducted by ECHA          | --                                                                                                                                                                      |
| Critical study                                                                                                 | ECHA, 2020                                                                     | --                                                                                                                                                                      |
| Species                                                                                                        | Rats                                                                           | --                                                                                                                                                                      |
| Target Organ                                                                                                   | Liver, skin, developmental                                                     | --                                                                                                                                                                      |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Skin encrustations, sparsely haired areas, and encrustations around the eyes). | No statistically significant developmental findings                                                                                                                     |
| Other Endpoints                                                                                                | --                                                                             | --                                                                                                                                                                      |
| Uncertainty Factors                                                                                            | Total UF = 3 x 10 x 10 x 10 = 3000                                             | UF (animal to human) = 3<br>UF (sensitive humans) = 10<br>UF (subchronic to chronic) = 10<br>UF (data insufficiency) = 10                                               |
| POD Method                                                                                                     | NOAEL                                                                          | NOAEL = 5 mg/kgBW/day                                                                                                                                                   |
| Human Equivalent Concentration in TRV?                                                                         | Yes                                                                            | A human equivalent dose (NOAEL <sub>HED</sub> ) is calculated from the rats using a dosimetric adjustment factor (DAF) based on the human to animal body weight ratios. |
| Duration of exposure                                                                                           | 90-days                                                                        | --                                                                                                                                                                      |
| Time Adjustment in TRV?                                                                                        | Yes, annual time averaging                                                     | --                                                                                                                                                                      |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Developmental or Reproductive Effects? | Developmental and reproductive studies with mixed results. "The higher T4 levels in male pups in low- and mid-dose groups could be indicative of an adverse effect at the 5 mg/kg (low-dose) group."                                                                                                                                                                                                                                     |
| Oral to inhalation extrapolation       | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Additional notes                       | Chronic ITSL = $RfD \times \text{body weight/daily inhalation rate} \times \text{unit conversion}$<br>Chronic ITSL = $0.00039 \text{ mg/kgBW/day} \times 70\text{kg}/20\text{m}^3 \times 1000\mu\text{g/mg}$<br>Chronic ITSL = $1.37 \mu\text{g/m}^3$<br>Chronic ITSL = $1 \mu\text{g/m}^3$ ; rounded to 1 significant figure                                                                                                            |
| Links to TRV Sources                   | <a href="https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=27619972&amp;cmdSubmit=Submit">https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=27619972&amp;cmdSubmit=Submit</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/27619-97-2/27619-97-2_annual_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/27619-97-2/27619-97-2_annual_ITSL.pdf</a> |

#### 4.15.2. ECHA

TABLE 54. ECHA OCCUPATIONAL DNEL FOR 6:2 FTS (CAS 27619-97-2)

| Variable                                                                                                       | Value                                                                                                  | Comment                                                                                     |
|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Occupational Long-term DNEL                                                                                    | $1,080 \mu\text{g/m}^3$ ( $1.08 \text{ mg/m}^3$ )                                                      | Derived No Effect Level                                                                     |
| Date                                                                                                           | September 26, 2019                                                                                     | Derived No Effect Level                                                                     |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Combined repeated oral dose toxicity study with the reproduction/developmental toxicity screening test | --                                                                                          |
| Critical study                                                                                                 | Key study not named                                                                                    | --                                                                                          |
| Species                                                                                                        | Rat                                                                                                    | --                                                                                          |
| Target Organ                                                                                                   | Kidney                                                                                                 | --                                                                                          |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Mild to moderate multifocal tubular dilatation                                                         | --                                                                                          |
| Other Endpoints                                                                                                | --                                                                                                     | --                                                                                          |
| Assessment Factors                                                                                             | Total AF = $2 \times 2.5 \times 5 = 25$                                                                | AF (subchronic to chronic) = 2<br>AF (oral to inhalation) = 2.5<br>AF (animal to human) = 5 |
| POD Method                                                                                                     | NOAEL                                                                                                  | NOAEL = $15 \text{ mg/kg bw/day}$<br>LOEC = $45 \text{ mg/kg bw/day}$                       |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                         |
|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Equivalent Concentration in TRV? | Original NOAEL = 15 mg/kg bw/day<br>Corrected NOAEL = 15 mg/kg bw/day * (1/0.38 m <sup>3</sup> /kg/day) * 6.7m <sup>3</sup> /10m <sup>3</sup> = 26.45 mg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Calculated using R.8.4.2 of ECHA guidelines:<br><a href="https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258">https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258</a> |
| Duration of exposure                   | 90 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | --                                                                                                                                                                                                                                                                                                      |
| Time Adjustment in TRV?                | Through Assessment Factors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | --                                                                                                                                                                                                                                                                                                      |
| Developmental or Reproductive Effects? | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | --                                                                                                                                                                                                                                                                                                      |
| Oral to inhalation extrapolation       | Accounted for in UF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                         |
| Additional notes                       | Long-term DNEL = Corrected NOAEL / Total AF = 26.45/25 = 1.06 mg/m <sup>3</sup><br>(Note DNEL set at 1.08, unclear why there is a difference).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                         |
| Links to TRV Sources                   | Dossier: <a href="https://chem.echa.europa.eu/100.044.149/dossier-view/618aa105-1c47-4bc7-9633-bb54ae800bcd/b4ff75f2-02a8-43b2-8ab3-86580b6aaf07_96ab02e6-6a70-4f8e-b823-912bd773ffad?searchText=27619-97-2">https://chem.echa.europa.eu/100.044.149/dossier-view/618aa105-1c47-4bc7-9633-bb54ae800bcd/b4ff75f2-02a8-43b2-8ab3-86580b6aaf07_96ab02e6-6a70-4f8e-b823-912bd773ffad?searchText=27619-97-2</a><br><br>ECHA Calculation Guidelines:<br><a href="https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258">https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258</a> |                                                                                                                                                                                                                                                                                                         |

#### 4.16. Hexafluoropropylene oxide dimer acid (HFPO-DA/Gen-X) (CAS 62037-80-3)

ERG identified non-carcinogenic health-based screening values for HFPO-DA/Gen-X. The identified values come from New Jersey and ECHA and range from 0.01 to 140 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental and reproductive effects were observed for HFPO-DA/Gen-X in TRV source documents.

HFPO-DA/Gen-X is not present on the DOT list of inhalation hazards.

TABLE 55. INHALATION TRVs FOR HFPO-DA/GEN-X (CAS 62037-80-3)

| State/Agency   | TRV                     | TRV                                             | Classification      | DEQ Notes                                         |
|----------------|-------------------------|-------------------------------------------------|---------------------|---------------------------------------------------|
| New Jersey DEP | RfC                     | 0.01 µg/m <sup>3</sup>                          | Non-cancer, chronic | Unmodified                                        |
| ECHA           | Occupational DNEL       | 140 µg/m <sup>3</sup> (0.14 mg/m <sup>3</sup> ) | Non-cancer, chronic | Derivation not transparent and occupational value |
|                | General Population DNEL | 40 µg/m <sup>3</sup> (0.04 mg/m <sup>3</sup> )  | Non-cancer, chronic | Derivation not transparent                        |

#### 4.16.1. New Jersey DEP

TABLE 56. NEW JERSEY DEP ITSL / RfC FOR HFPO-DA/GEN-X (CAS 62037-80-3)

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                          | Comment                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| RfC                                                                                                            | 0.01 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                         | --                                                                                                                                          |
| Date                                                                                                           | January 25, 2022                                                                                                                                                                                                                                                                                               |                                                                                                                                             |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Oral reproductive and developmental mouse study                                                                                                                                                                                                                                                                | Adopted USEPA assessment and RfD of 3 ng/kg/day                                                                                             |
| Critical study                                                                                                 | DuPont-18405-1037. (2010). An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice. U.S. EPA OPPTS 870.3550; OECD Test Guideline 421. E.I. du Pont de Nemours and Company. Study conducted by WIL Research Laboratories, LLC (Study Completed: December 29, 2010), Ashland, OH | As assessed by USEPA Toxicity Assessment of GenX                                                                                            |
| Species                                                                                                        | Mouse                                                                                                                                                                                                                                                                                                          |                                                                                                                                             |
| Target Organ                                                                                                   | Liver                                                                                                                                                                                                                                                                                                          |                                                                                                                                             |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Combined incidence of several histopathological changes                                                                                                                                                                                                                                                        |                                                                                                                                             |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                                                                                                                             | --                                                                                                                                          |
| Uncertainty Factors                                                                                            | Total UF for RfD = 3 x 10 x 10 x 10 = 3000                                                                                                                                                                                                                                                                     | Animal to human UF = 3<br>Sensitive individuals UF = 10<br>Subchronic to chronic UF = 10<br>Data insufficiency UF = 10                      |
| POD Method                                                                                                     | BMDL10                                                                                                                                                                                                                                                                                                         | BMDL10 = 0.09 mg/kg/day                                                                                                                     |
| Human Equivalent Concentration in TRV?                                                                         | POD <sub>HED</sub> of 0.01 mg/kg/day                                                                                                                                                                                                                                                                           | Dose to animals (ng/kg/day) x dosimetric adjustment factor (DAF) (unitless) = HED (ng/kg/day)<br><br>0.09 mg/kg/day x 0.14 = 0.01 mg/kg/day |
| Duration of exposure                                                                                           | F0 female mice: Daily doses 2 weeks prior to mating through LD20 (total of 53-64 days).                                                                                                                                                                                                                        | --                                                                                                                                          |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Time Adjustment in TRV?                | No expected duration adjustment, but sub-chronic to chronic UF applied.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -- |
| Developmental or Reproductive Effects? | Developmental and Reproductive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |
| Oral to inhalation extrapolation       | <p> <math>POD \text{ (mg/kg/day)} / UF = RfD \text{ (mg/kg/day)}</math><br/> <math>0.01 \text{ mg/kg/day} / 3000 = 3 \times 10^{-6} \text{ mg/kg/day}</math> </p> <p> <math>RfC \text{ (}\mu\text{g/m}^3\text{)} = RfD \text{ (}\mu\text{g/kg/day)} \times [(\text{body weight, kg}) \div (\text{inhalation rate per day, m}^3\text{/day})]</math> </p> <p> <math>RfC = 0.003 \text{ }\mu\text{g/kg/day} * (70\text{kg}) / (20 \text{ m}^3\text{/day}) = 0.01 \text{ }\mu\text{g/m}^3</math> </p>                                                                                                                                                                                                                                                                                |    |
| Additional notes                       | Based on USEPA Toxicity Assessment for Genx.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |
| Links to TRV Sources                   | <p> <a href="https://dep.nj.gov/wp-content/uploads/dsr/hfpo-da-genx-tsd.pdf">https://dep.nj.gov/wp-content/uploads/dsr/hfpo-da-genx-tsd.pdf</a> </p> <p>USEPA, 2021. Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3), Also Known as "GenX Chemicals". U.S. Environmental Protection Agency Office of Water (4304T), Health and Ecological Criteria Division Washington, DC 20460. EPA Document Number: 822R-21-010. October 2021. <a href="https://www.epa.gov/system/files/documents/2021-10/genx-chemicals-toxicity-assessment_tech-edited_oct-21-508.pdf">https://www.epa.gov/system/files/documents/2021-10/genx-chemicals-toxicity-assessment_tech-edited_oct-21-508.pdf</a></p> |    |

#### 4.16.2. ECHA

TABLE 57. ECHA OCCUPATIONAL AND LONG-TERM DNEL FOR HFPO-DA/GEN-X (CAS 62037-80-3)

| Variable                                                                                                       | Value                                           | Comment                 |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------|-------------------------|
| Occupational Long-term DNEL                                                                                    | 140 $\mu\text{g/m}^3$ (0.14 mg/m <sup>3</sup> ) | Derived No Effect Level |
| General Population Long-term DNEL                                                                              | 40 $\mu\text{g/m}^3$ (0.04 mg/m <sup>3</sup> )  | Derived No Effect Level |
| Date                                                                                                           | May 31, 2022                                    | --                      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Chronic oral toxicity study                     | --                      |

|                                                                   |                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | Confidential Dupont study Not publicly available                                                                                                | <p>According to ECHA: “The key study for DNEL calculation is an OECD 453 rat chronic toxicity study via oral administration.”</p> <p><a href="https://chem.echa.europa.eu/100.124.803/dossier-view/44e19448-3d8b-41cd-8d89-135229e77d95/IUC5-6d5b492b-6918-42cb-8907-3e5677c2df4d_30e1ec53-b1c5-4c8e-987c-453439169baa">https://chem.echa.europa.eu/100.124.803/dossier-view/44e19448-3d8b-41cd-8d89-135229e77d95/IUC5-6d5b492b-6918-42cb-8907-3e5677c2df4d_30e1ec53-b1c5-4c8e-987c-453439169baa</a></p>                                  |
| Species                                                           | Rat                                                                                                                                             | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Target Organ                                                      | Liver                                                                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Description of TRV endpoints/ basis for points of departure (POD) | Focal cystic degeneration, focal necrosis, and centrilobular necrosis of the liver, with associated increases in cytotoxic liver enzymes        | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Other Endpoints                                                   | Pancreatic acinar cell tumours and testicular interstitial (Leydig) cell tumours                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Assessment Factors                                                | <p>Total AF(workers) = <math>2.5 \times 5 = 12.5</math></p> <p>Total AF (general population) = <math>2.5 \times 5 \times 10 = 25</math></p>     | <p>AF (oral to inhalation) = 2.5</p> <p>AF (animal to human, workers) = 5</p> <p>AF (animal to human, general population) = 10</p>                                                                                                                                                                                                                                                                                                                                                                                                        |
| POD Method                                                        | NOAEC                                                                                                                                           | NOAEL = $1.0 \text{ mg/m}^3$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Human Equivalent Concentration in TRV?                            | <p><math>\text{NOAEL}_{\text{workers}} = 1.76 \text{ mg/m}^3</math></p> <p><math>\text{NOAEL}_{\text{general}} = 0.87 \text{ mg/m}^3</math></p> | <p><math>\text{NOAEL}_{\text{workers}} = \text{NOAEL} * 1/0.38 \text{ m}^3 * 0.67</math></p> <p>Where,</p> <p><math>1/0.38 \text{ m}^3</math> is the standard respiratory volume conversion from rat to human, and</p> <p>0.67 is the increased respiratory volume in active workers as compared to individuals at rest</p> <p><math>\text{NOAEL}_{\text{general}} = \text{NOAEL} * 1/1.15 \text{ m}^3</math></p> <p>Where, <math>1/1.15 \text{ m}^3</math> is the conversion factor for 24-hour respiratory volume from rat to human</p> |
| Duration of exposure                                              | Daily exposure for up to 104 weeks (males) or 101 weeks (females)                                                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Time Adjustment in TRV?                                           | Unclear                                                                                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Developmental or Reproductive Effects?                            | No                                                                                                                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral to inhalation extrapolation | "Since the substance was determined to be completely absorbed from the gastrointestinal tract, no modification of the starting point was needed to correct for oral administration as compared to inhalation."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Additional notes                 | $DNEL_{workers} = NOAEL_{workers} / AF_{workers} = 1.76 \text{ mg/m}^3 / 12.5 = 0.14 \text{ mg/m}^3$<br>$DNEL_{general} = NOAEL_{general} / AF_{general} = 0.87 \text{ mg/m}^3 / 25 = 0.04 \text{ mg/m}^3$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Links to TRV Sources             | <p>ECHA Calculation Guidelines:<br/> <a href="https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258">https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258</a></p> <p>Dossier: <a href="https://chem.echa.europa.eu/100.124.803/dossier-view/44e19448-3d8b-41cd-8d89-135229e77d95/f3fb00e0-3ca7-42c5-8b37-3b37b4127349_f3fb00e0-3ca7-42c5-8b37-3b37b4127349?searchText=62037-80-3">https://chem.echa.europa.eu/100.124.803/dossier-view/44e19448-3d8b-41cd-8d89-135229e77d95/f3fb00e0-3ca7-42c5-8b37-3b37b4127349_f3fb00e0-3ca7-42c5-8b37-3b37b4127349?searchText=62037-80-3</a></p> |

#### 4.17. Perfluorobutylethylene (PFBE) (CAS 19430-93-4)

ERG identified non-carcinogenic health-based screening values for PFBE. The identified values come from Michigan and ECHA and range from 2,600  $\mu\text{g/m}^3$  to 1,031,400  $\mu\text{g/m}^3$  (1,031.4  $\text{mg/m}^3$ ). Cancer screening values were not identified.

Developmental and reproductive effects were observed for PFBE in various TRV source documents.

PFBE is not present on the DOT list of inhalation hazards.

TABLE 58. INHALATION TRVs FOR PERFLUOROBUTYLETHYLENE (PFBE) (CAS 19430-93-4)

| State/Agency  | TRV                     | TRV                                                     | Classification      | DEQ Notes                                           |
|---------------|-------------------------|---------------------------------------------------------|---------------------|-----------------------------------------------------|
| Maryland DE   | 8-hour* Screening Level | 10,065.4 $\mu\text{g/m}^3$                              | Non-cancer, chronic | Derived from occupational                           |
| Michigan EGLE | 8-Hour ITSL**           | 10,000 $\mu\text{g/m}^3$                                | Non-cancer, chronic | Derived from occupational                           |
|               | Annual ITSL             | 2,600 $\mu\text{g/m}^3$                                 | Non-cancer, chronic | Unmodified                                          |
| ECHA          | Occupational DNEL       | 1,031,400 $\mu\text{g/m}^3$ (1,031.4 $\text{mg/m}^3$ ). | Non-cancer, chronic | Derived from and for occupational exposures         |
|               | General Population DNEL | 256,600 $\mu\text{g/m}^3$ (256.6 $\text{mg/m}^3$ )      | Non-cancer, chronic | Not transparently derived – no critical study named |

\* Calculated from an occupational exposure limit that assumes an 8-hour workday and a 40-hour workweek

\*\* Described as 'short-term' by EGLE compared to 'annual' ITSL; however, calculated from ACIGH TLV based on 8-hour workday assumptions.

#### 4.17.1. Maryland DE

**TABLE 59. MARYLAND DE 8-HOUR SCREENING LEVEL FOR PFBE (CAS 19430-93-4)**

| Variable                                                                                                       | Value                                                                                                                                                                                                                                                                                                                                                                                                                           | Comment                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 8-hour Screening Level                                                                                         | 10,065.4 $\mu\text{g}/\text{m}^3$                                                                                                                                                                                                                                                                                                                                                                                               | Non-carcinogenic, 8-hour screening level. Calculated from a TLV-TWA, “for a conventional 8-hour workday and a 40-hour workweek” |
| Date                                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                              | Calculated from an ACGIH TLV but year/date not provided.                                                                        |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit                                                                                                                                                                                                                                                                                                                                                                                                     | Calculated from an ACGIH TLV.                                                                                                   |
| Critical study                                                                                                 | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Species                                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Target Organ                                                                                                   | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Uncertainty Factors                                                                                            | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| POD Method                                                                                                     | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Human Equivalent Concentration in TRV?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Duration of exposure                                                                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Time Adjustment in TRV?                                                                                        | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Developmental or Reproductive Effects?                                                                         | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Oral to inhalation extrapolation?                                                                              | --                                                                                                                                                                                                                                                                                                                                                                                                                              | No information on derivation.                                                                                                   |
| Additional notes                                                                                               | <p>ERG reached out to Maryland DE to obtain the Agency’s current TRV values and their derivations. MDE responded by noting that the TRV was set by the ACGIH TLV. Other information was not provided.</p> <p>According to regulation: “If a toxic air pollutant (TAP) has a threshold limit value-time weighted average (TLV-TWA), divide the TLV-TWA by 100 to calculate an 8-hour time-weighted average screening level”.</p> |                                                                                                                                 |



|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://mde.maryland.gov/programs/permits/airmanagementpermits/page/s/toxicairpollutantregulationdocuments.aspx">https://mde.maryland.gov/programs/permits/airmanagementpermits/page/s/toxicairpollutantregulationdocuments.aspx</a><br><br><a href="https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03">https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03</a><br><br>(see email from MDE). |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### 4.17.2. Michigan EGLE

TABLE 60. MICHIGAN EGLE 8-HOUR AND ANNUAL ISTL FOR PFBE (CAS 19430-93-4)

| Variable                                                                                                       | Value                                                                                                                                                                   | Comment                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8-Hour ITSL                                                                                                    | 10,000 µg/m <sup>3</sup>                                                                                                                                                | 8-hour averaging time ITSL                                                                                                                                  |
| Annual ITSL                                                                                                    | 2,600 µg/m <sup>3</sup>                                                                                                                                                 | annual averaging time ITSL                                                                                                                                  |
| Date                                                                                                           | July 9, 2021                                                                                                                                                            | --                                                                                                                                                          |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Short-term ITSL: Occupational Exposure limit derived a TWA for PFBE of 100 ppm based on hematological effects in 2001<br><br>Long-term ITSL: ECHA rat inhalation study. | Short-term: ACGIH TWA                                                                                                                                       |
| Critical study                                                                                                 | Long-term: ECHA 2021 Study report dated 2001                                                                                                                            | Short-term: ACGIH TWA, unclear of original study                                                                                                            |
| Species                                                                                                        | Long-term: Rat                                                                                                                                                          | Short-term: Unclear original study                                                                                                                          |
| Target Organ                                                                                                   | Short-term: Hematological system<br>Long-term: Respiratory                                                                                                              | --                                                                                                                                                          |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Short-term: Hematological effects<br>Long-term: Congestion and weight loss                                                                                              | --                                                                                                                                                          |
| Other Endpoints                                                                                                | Additional chronic endpoints: urine chemistry changes, kidney, and liver changes                                                                                        |                                                                                                                                                             |
| Uncertainty Factors                                                                                            | Short-term: 100<br><br>Long-term: "Safety Factors" = 20 x 10 x 10 = 2000                                                                                                | Short-term: unclear source of 100 in formula.<br><br>Long-term:<br>UF (subacute to chronic) = 20<br>UF (animal to human) = 10<br>UF (sensitive humans) = 10 |
| POD Method                                                                                                     | Short-term: OEL<br>Long-term: NOAEC                                                                                                                                     | Short-term ITSL = OEL/100<br>Long-term ITSL = NOAEC / SF *<br>Dosimetric Adjustment                                                                         |
| Human Equivalent Concentration in TRV?                                                                         | Short-term ITSL: No<br>Long-term ITSL: Yes                                                                                                                              | --                                                                                                                                                          |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                  |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Duration of exposure                   | Short-term: Single exposure<br>Long-term: 28 consecutive days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                  |
| Time Adjustment in TRV?                | Short-term ITSL: No<br>Long-term ITSL: Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Long-term: Dosimetric adjustment of 6 hours exposed per day divided by 24 hours. |
| Developmental or Reproductive Effects? | A developmental study was discussed in the supporting documentation, but “no treatment-related fetal effects” were observed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                  |
| Oral to inhalation extrapolation       | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                  |
| Additional notes                       | <p><u>Short-term:</u><br/>ACGIH OEL = 100 ppm<br/>ITSL = OEL/100</p> <p>ppm to <math>\mu\text{g}/\text{m}^3</math>:<br/> <math display="block">Y \mu\text{g}/\text{m}^3 = (100 \text{ ppm})(246.076)/(24.45) \times 1000 \mu\text{g}/\text{m}^3 = 1.0 \times 10^6 \mu\text{g}/\text{m}^3</math> (rounded)</p> <p>ITSL = <math>1,000,000/100 = 10,000 \mu\text{g}/\text{m}^3</math></p> <p><u>Annual:</u><br/>NOAEC = <math>2069 \text{ ppm} \times 6 \text{ hours}/24 \text{ hours} = 517 \text{ ppm}</math></p> <p>PPM to <math>\mu\text{g}/\text{m}^3</math>:<br/> <math display="block">Y \mu\text{g}/\text{m}^3 = (X \text{ ppm})(\text{molecular weight})/24.45 \times 1000 \mu\text{g}/\text{mg}</math> <math display="block">Y \mu\text{g}/\text{m}^3 = (517 \text{ ppm})(246.076 \text{ MW})/24.45 \times 1000 \mu\text{g}/\text{mg} = 5.2 \times 10^6 \mu\text{g}/\text{m}^3</math></p> <p>Annual ITSL = <math>5.2 \times 10^6 \mu\text{g}/\text{m}^3 / \text{UFs}</math><br/> Annual ITSL = <math>5.2 \times 10^6 \mu\text{g}/\text{m}^3 / (20 \times 10 \times 10) = 2600 \mu\text{g}/\text{m}^3</math> (annual)</p> |                                                                                  |
| Links to TRV Sources                   | <a href="https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=19430934&amp;cmdSubmit=Submit">https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=19430934&amp;cmdSubmit=Submit</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/19430-93-4/19430-93-4_annual_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/19430-93-4/19430-93-4_annual_ITSL.pdf</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                  |

#### 4.17.3. ECHA

TABLE 61. ECHA OCCUPATIONAL AND GENERAL POPULATION DNEL FOR PFBE (CAS 19430-93-4)

| Variable                          | Value                           | Comment                 |
|-----------------------------------|---------------------------------|-------------------------|
| Occupational Long-term DNEL       | $1,031.4 \text{ mg}/\text{m}^3$ | Derived No Effect Level |
| General Population Long-term DNEL | $256.6 \text{ mg}/\text{m}^3$   | Derived No Effect Level |
| Date                              | June 26, 2017                   | --                      |

|                                                                                                                |                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Inhalation toxicity study                                                                                                                                                                          | --                                                                                                                                                                                                                                                                                                                           |
| Critical study                                                                                                 | Key study not named                                                                                                                                                                                | --                                                                                                                                                                                                                                                                                                                           |
| Species                                                                                                        | Rat                                                                                                                                                                                                | --                                                                                                                                                                                                                                                                                                                           |
| Target Organ                                                                                                   | --                                                                                                                                                                                                 | --                                                                                                                                                                                                                                                                                                                           |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | Total white blood cell count reduction; reduction in body weight gain [neither considered toxicologically significant]                                                                             | --                                                                                                                                                                                                                                                                                                                           |
| Other Endpoints                                                                                                | --                                                                                                                                                                                                 | --                                                                                                                                                                                                                                                                                                                           |
| Assessment Factors                                                                                             | $\text{Total AF}_{\text{workers}} = 2 \times 2.5 \times 5 \times 2 = 50$<br>$\text{Total AF}_{\text{general}} = 2 \times 2.5 \times 10 \times 2 = 100$                                             | AF (subchronic to chronic) = 2<br>AF (animal to human) = 2.5<br>AF (sensitive individuals, workers) = 5<br>AF (sensitive individuals, general population) = 10<br>AF (data insufficiency) = 2                                                                                                                                |
| POD Method                                                                                                     | $\text{NOAEC} = 102,625.8 \text{ mg/m}^3$                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                              |
| Human Equivalent Concentration in TRV?                                                                         | $\text{Corrected NOAEL}_{\text{workers}} = 102625.8 \times 0.67 \times 0.75 = 51569.5 \text{ mg/m}^3$<br>$\text{Corrected NOAEL}_{\text{general}} = 102625.8 \times 0.25 = 25656.5 \text{ mg/m}^3$ | <u>Workers:</u><br>Correct for respiratory volume (from resting rat to active human): $6.7 \text{ m}^3 / 10 \text{ m}^3 = 0.67$<br><br>Correct for exposure time (from 6 hour rat to 8 hour human): $6 / 8 = 0.75$<br><br><u>General population:</u><br>Correct for exposure from 6 hour rat to 24 hour human: $6/24 = 0.25$ |
| Duration of exposure                                                                                           | 90 days, 6 hours/day for 5 days/week                                                                                                                                                               | --                                                                                                                                                                                                                                                                                                                           |
| Time Adjustment in TRV?                                                                                        | Subchronic to chronic UF                                                                                                                                                                           | --                                                                                                                                                                                                                                                                                                                           |
| Developmental or Reproductive Effects?                                                                         | No                                                                                                                                                                                                 | --                                                                                                                                                                                                                                                                                                                           |
| Oral to inhalation extrapolation                                                                               | No                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                              |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | <p>Occupational DNEL = Corrected NOAEL<sub>workers</sub> / AF<sub>workers</sub> = 51569.5 mg/m<sup>3</sup> / 50 = 1,031.4 mg/m<sup>3</sup></p> <p>General Population DNEL = Corrected NOAEL<sub>general</sub> / AF<sub>general</sub> = 25656.5 mg/m<sup>3</sup> / 100 = 256.6 mg/m<sup>3</sup></p> <p>“At the time of registration a proposal was submitted to ECHA to perform a 90 -day (subchronic) study by inhalation in the rat, which was accepted. The study has now been completed and is reported in the update. The NOAEC in this 90 -day study is 102,625.8 mg/m<sup>3</sup> (10,200 ppm). This is an increase in NOAEC when compared to the previous key study, a 28 -day inhalation study in rat (NOAEC 20123.0 mg/m<sup>3</sup>) (DuPont Study Number 02 G01001). Moreover, histopathological changes that were observed in the larynx, lungs and the liver of rats exposed to 9879 ppm in the 28 -day study, which at the time were thought to be treatment related, were not observed in the 90 -day study. As a result the DNEL is revised accordingly.”</p> |
| Links to TRV Sources | <p>Dossier: <a href="https://chem.echa.europa.eu/100.039.124/dossier-view/e817a741-c3b7-4675-a2fc-8fe904f3d7cc/6dccbce2-14c2-4023-b848-b9f405a09134_de42cf1b-213b-46f9-b438-8258d9fef067?searchText=19430-93-4">https://chem.echa.europa.eu/100.039.124/dossier-view/e817a741-c3b7-4675-a2fc-8fe904f3d7cc/6dccbce2-14c2-4023-b848-b9f405a09134_de42cf1b-213b-46f9-b438-8258d9fef067?searchText=19430-93-4</a></p> <p>ECHA Calculation Guidelines:<br/><a href="https://echa.europa.eu/documents/10162/13632/information_requirement_s_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258">https://echa.europa.eu/documents/10162/13632/information_requirement_s_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258</a></p>                                                                                                                                                                                                                                                                                                                                                           |

#### 4.18. Perfluoroisobutene (PFIB) (CAS 382-21-8)

ERG identified non-carcinogenic health-based screening values for PFIB. The identified values come from Maryland, Michigan, and Wisconsin and range from 0.8 to 8.18 µg/m<sup>3</sup>. Cancer screening values were not identified.

Developmental and reproductive effects were not observed for PFBE in TRV source documents.

PFIB is not present on the DOT list of inhalation hazards.

DEQ does not propose to establish a TRV for this TAC. No suitable values available.

TABLE 62. INHALATION TRVs FOR PERFLUOROISOBUTYLENE (PFIB) (CAS 382-21-8)

| State/Agency  | TRV                     | TRV                    | Classification      | DEQ Notes                 |
|---------------|-------------------------|------------------------|---------------------|---------------------------|
| Maryland DE   | 1-Hour Screening Level  | 0.82 µg/m <sup>3</sup> | Non-cancer, acute   | Derived from occupational |
|               | 8-Hour Screening Level* | 0.41 µg/m <sup>3</sup> | Non-cancer, chronic | Derived from occupational |
| Michigan EGLE | 1-Hour ITSL             | 0.8 µg/m <sup>3</sup>  | Non-cancer, acute   | Derived from occupational |

|               |                             |                        |                   |                           |
|---------------|-----------------------------|------------------------|-------------------|---------------------------|
| Wisconsin DNR | 1-Hour Ambient Air Standard | 8.18 µg/m <sup>3</sup> | Non-cancer, acute | Derived from occupational |
|---------------|-----------------------------|------------------------|-------------------|---------------------------|

\*\* Calculated from an occupational exposure limit that assumes an 8-hour workday and a 40-hour workweek

#### 4.18.1. Maryland DE

TABLE 63. MARYLAND DE 8-HOUR SCREENING LEVEL FOR PFIB (CAS 382-21-8)

| Variable                                                                                                       | Value                                               | Comment                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| 1hr Screening Level                                                                                            | 0.82 µg/m <sup>3</sup>                              | Non-carcinogenic, 1-hour screening level. Calculated from a ceiling TLV (TLV-C) or a short term exposure limit (TLV-STEL).      |
| 8hr Screening Level                                                                                            | 0.41 µg/m <sup>3</sup>                              | Non-carcinogenic, 8-hour screening level. Calculated from a TLV-TWA, “for a conventional 8-hour workday and a 40-hour workweek” |
| Date                                                                                                           | --                                                  | Year/date of derivation or study not provided.                                                                                  |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | 1-hour: Occupational Exposure Limit<br>8-hour: LC50 | 1-hour: ACGIH ceiling TLV (TLV-C) or a short-term exposure limit (TLV-STEL),<br>8-hour: Calculated from an LC50 approach.       |
| Critical study                                                                                                 | --                                                  | No information on derivation.                                                                                                   |
| Species                                                                                                        | --                                                  | No information on derivation.                                                                                                   |
| Target Organ                                                                                                   | --                                                  | No information on derivation.                                                                                                   |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                                                  | No information on derivation.                                                                                                   |
| Other Endpoints                                                                                                | --                                                  | No information on derivation.                                                                                                   |
| Uncertainty Factors                                                                                            | --                                                  | No information on derivation.                                                                                                   |
| POD Method                                                                                                     | --                                                  | No information on derivation.                                                                                                   |
| Human Equivalent Concentration in TRV?                                                                         | --                                                  | No information on derivation.                                                                                                   |
| Duration of exposure                                                                                           | --                                                  | No information on derivation.                                                                                                   |
| Time Adjustment in TRV?                                                                                        | --                                                  | No information on derivation.                                                                                                   |
| Developmental or Reproductive Effects?                                                                         | --                                                  | No information on derivation.                                                                                                   |
| Oral to inhalation extrapolation?                                                                              | --                                                  | No information on derivation.                                                                                                   |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Additional notes     | <p>ERG reached out to Maryland DE to obtain the Agency's current TRV values and their derivations. MDE responded by noting that the 8-hour screening level was set by an LC50, and the 1-hour screening level was set by an ACGIH value. Other information was not provided.</p> <p>According to regulation, to calculate an 8-hour screening level: "If a TAP has neither a TLV, nor a special screening level, nor an acceptable ambient level,... Divide an LC50 in milligrams/cubic meter for rats, mice, or rabbits by 10,000".</p> <p>For a 1-hour screening level: "If a TAP has a ceiling TLV (TLV-C) or a short term exposure limit (TLV-STEL), divide the TLV-C or TLV-STEL by 100 to calculate a 1-hour time-weighted average screening level"</p> |
| Links to TRV Sources | <p><a href="https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx">https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx</a></p> <p><a href="https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03">https://www.law.cornell.edu/regulations/maryland/COMAR-26-11-16-03</a></p> <p>(see email from MDE).</p>                                                                                                                                                                                                                                                                                                                    |

#### 4.18.2. Michigan EGLE

TABLE 64. MICHIGAN EGLE ITSL FOR PFIB (CAS 382-21-8)

| Variable                                                                                                       | Value                       | Comment                                                                                         |
|----------------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------|
| ITSL                                                                                                           | 0.8 µg/m <sup>3</sup>       | 1-hour averaging time                                                                           |
| Date                                                                                                           | August 1, 2003              | Based on ACGIH value from 1992                                                                  |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit | ACGIH TLV-Ceiling value of 0.01 ppm (0.082 mg/m <sup>3</sup> )                                  |
| Critical study                                                                                                 | NA – ACGIH value            | No information on derivation.                                                                   |
| Species                                                                                                        | --                          | No information on derivation.                                                                   |
| Target Organ                                                                                                   | --                          | No information on derivation.                                                                   |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                          | No information on derivation.                                                                   |
| Other Endpoints                                                                                                | --                          | No information on derivation.                                                                   |
| Uncertainty Factors                                                                                            | 100                         | Factor of 1/100 included in regulatory formula when using OEL. No explanation of source of 100. |
| POD Method                                                                                                     | --                          | No information on derivation.                                                                   |
| Human Equivalent Concentration in TRV?                                                                         | --                          | No information on derivation.                                                                   |

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                        |                               |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Duration of exposure                   | --                                                                                                                                                                                                                                                                                                                                                                                                                     | No information on derivation. |
| Time Adjustment in TRV?                | --                                                                                                                                                                                                                                                                                                                                                                                                                     | No information on derivation. |
| Developmental or Reproductive Effects? | --                                                                                                                                                                                                                                                                                                                                                                                                                     | No information on derivation. |
| Oral to inhalation extrapolation       | --                                                                                                                                                                                                                                                                                                                                                                                                                     | No information on derivation. |
| Additional notes                       | ITSL = OEL/100 = 0.082 mg/m <sup>3</sup> / 100 = 0.8 µg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                 |                               |
| Links to TRV Sources                   | <a href="https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=382218&amp;cmdSubmit=Submit">https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=382218&amp;cmdSubmit=Submit</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/382-21-8/382-21-8_1hr_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/382-21-8/382-21-8_1hr_ITSL.pdf</a> |                               |

#### 4.18.3. Wisconsin DNR

Table 65. Wisconsin DNR 1-hour Ambient Air Standard for PFIB (CAS 382-21-8)

| Variable                                                                                                       | Value                       | Comment                                     |
|----------------------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------|
| 1-hour AAL                                                                                                     | 8.18 µg/m <sup>3</sup>      | --                                          |
| Date                                                                                                           | --                          | Not clear when added to list.               |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Occupational Exposure Limit | ACGIH's TLV and biological indices for 2000 |
| Critical study                                                                                                 | --                          | --                                          |
| Species                                                                                                        | --                          | No information on derivation.               |
| Target Organ                                                                                                   | --                          | No information on derivation.               |
| Description of TRV endpoints/ basis for points of departure (POD)                                              | --                          | No information on derivation.               |
| Other Endpoints                                                                                                | --                          | No information on derivation.               |
| Uncertainty Factors                                                                                            | --                          | No information on derivation.               |
| POD Method                                                                                                     | --                          | No information on derivation.               |
| Human Equivalent Concentration in TRV?                                                                         | --                          | No information on derivation.               |
| Duration of exposure                                                                                           | --                          | No information on derivation.               |
| Time Adjustment in TRV?                                                                                        | --                          | No information on derivation.               |
| Developmental or Reproductive Effects?                                                                         | -                           |                                             |

|                                  |                                                                                                                                                                                                                                                                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral to inhalation extrapolation | -                                                                                                                                                                                                                                                                                                                              |
| Additional notes                 | Wisconsin DNR provided information on derivation. 1-hour averaging time Ambient Air Standard set as 10% of the ACGIH 2000 TLV.<br><br>ACGIH 2000 TLV documentation not available.                                                                                                                                              |
| Links to TRV Sources             | See Email and documents from Wisconsin DNR<br><br><a href="http://docs.legis.wisconsin.gov/code/admin_code/nr/400/445.pdf">http://docs.legis.wisconsin.gov/code/admin_code/nr/400/445.pdf</a><br><br><a href="https://dnr.wisconsin.gov/topic/AirQuality/Rules.html">https://dnr.wisconsin.gov/topic/AirQuality/Rules.html</a> |

#### 4.19. Perfluorobutylethylmethyldichlorosilane (CAS 38436-16-7)

ERG identified a non-carcinogenic health-based screening value for Perfluorobutylethylmethyldichlorosilane. The identified value comes from Michigan EGLE. Cancer screening values were not identified.

Developmental and reproductive effects were not reported for Perfluorobutylethylmethyldichlorosilane in the Michigan EGL TRV source document.

Perfluorobutylethylmethyldichlorosilane is not present on the DOT list of inhalation hazards.

DEQ does not propose a TRV for this TAC. The only available tox value is from Michigan EGLE (below) and is based on an oral LD50 as the point of departure. DEQ considers this too uncertain to derive a TRV.

##### 4.19.1. Michigan EGLE

TABLE 66. MICHIGAN EGLE ISTL FOR PERFLUOROBUTYLETHYLMETHYLDICHLOROSILANE (CAS 38436-16-7)

| Variable                                                                                                       | Value                                                | Comment |
|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------|---------|
| ITSL                                                                                                           | 2 µg/m <sup>3</sup>                                  | Annual  |
| Date                                                                                                           | June 16, 2021                                        | --      |
| Source of TRV derivation (e.g., oral/inhalation study, occupational exposure limit, nontoxicological endpoint) | Acute oral toxicity studies in rats reported by ECHA | --      |



|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical study                                                    | ECHA, 2021                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | ECHA (European Chemical Authority). 2021. Dossier on Perfluorobutylethylmethyldichlorosilane. Available at: <a href="https://echa.europa.eu/registration-dossier/-/registered-dossier/21967">https://echa.europa.eu/registration-dossier/-/registered-dossier/21967</a> |
| Species                                                           | Rats                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | --                                                                                                                                                                                                                                                                      |
| Target Organ                                                      | Systemic, death                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | --                                                                                                                                                                                                                                                                      |
| Description of TRV endpoints/ basis for points of departure (POD) | Death                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -                                                                                                                                                                                                                                                                       |
| Other Endpoints                                                   | Lethargy, ataxia, righting response, piloerection, and prostration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | --                                                                                                                                                                                                                                                                      |
| Uncertainty Factors                                               | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ITSL formula divides LD50 by multiple factors but there is no explanation on what those factors are for: 1/500, 1/40, and 1/100 (see formula below).                                                                                                                    |
| POD Method                                                        | LD50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | --                                                                                                                                                                                                                                                                      |
| Human Equivalent Concentration in TRV?                            | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Unclear from formula if there is an explicit Human Equivalent concentration (see formula below).                                                                                                                                                                        |
| Duration of exposure                                              | Acute exposure (once)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | --                                                                                                                                                                                                                                                                      |
| Time Adjustment in TRV?                                           | --                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Unclear from formula if there is an explicit time adjustment (see formula below).                                                                                                                                                                                       |
| Developmental or Reproductive Effects?                            | No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -                                                                                                                                                                                                                                                                       |
| Oral to inhalation extrapolation                                  | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | (see notes below).                                                                                                                                                                                                                                                      |
| Additional notes                                                  | $ITSL = 1/500 \times 1/40 \times 1/100 \times (LD50 \text{ mg/kg} \times W_A) / (0.167 \times I_A)$ <p>LD50 = 890 mg/kg<br/> <math>W_A</math> = Body weight of the experimental animal in kilograms = 0.273-0.307 kg Initial wt.<br/> <math>I_A</math> = Daily inhalation rate of experimental animal in m<sup>3</sup>/day using Cal EPA regression model equation<br/> <math>I = 0.702 \times bw^{2/3}</math> in m<sup>3</sup>/day or <math>0.702 \times 0.273^{2/3} = 0.298 \text{ m}^3/\text{day}</math> and <math>0.702 \times 0.307^{2/3} = 0.322 \text{ m}^3/\text{day}</math> of 0.31 m<sup>3</sup>/day average</p> <p>Therefore: <math>ITSL = 1/500 \times 1/40 \times 1/100 \times (890 \text{ mg/kg} \times 0.29 \text{ kg}) / (0.167 \times 0.31 \text{ m}^3/\text{day}) = 0.00249 \text{ mg/m}^3</math> or <math>2 \text{ }\mu\text{g/m}^3</math> (rounded to 1 significant figure).</p> |                                                                                                                                                                                                                                                                         |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Links to TRV Sources | <a href="https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=38436167&amp;cmdSubmit=Submit">https://www.egle.state.mi.us/itslirsl/results.asp?Chemical_Name=&amp;CASNumber=38436167&amp;cmdSubmit=Submit</a><br><br><a href="https://www.egle.state.mi.us/aps/downloads/ATSL/38436-16-7/38436-16-7_annual_ITSL.pdf">https://www.egle.state.mi.us/aps/downloads/ATSL/38436-16-7/38436-16-7_annual_ITSL.pdf</a> |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## Appendix A – List of government agency websites reviewed for inhalation toxicity values

| State       | Agency                                                                                        | Website                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alabama     | Alabama Department of Environmental Management                                                | <a href="https://adem.alabama.gov/programs/air/airquality.cnt">https://adem.alabama.gov/programs/air/airquality.cnt</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Alaska      | Department of Environmental Conservation / Division of Air Quality                            | <a href="https://dec.alaska.gov/air/anpms/toxics/health/">https://dec.alaska.gov/air/anpms/toxics/health/</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Arizona     | Arizona Department of Environmental Quality                                                   | <a href="https://www.azdeq.gov/SIP">https://www.azdeq.gov/SIP</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Arkansas    | Arkansas Department of Energy and Environment / Office of Air Quality                         | <a href="https://www.adeq.state.ar.us/air/">https://www.adeq.state.ar.us/air/</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| California  | CalEPA<br><br>California Air Resources Board (CARB)<br><br>Department of Pesticide Regulation | <a href="https://oehha.ca.gov/air/general-info/toxic-air-contaminant-list-staff-reportsexecutive-summaries">https://oehha.ca.gov/air/general-info/toxic-air-contaminant-list-staff-reportsexecutive-summaries</a><br><br><a href="https://ww2.arb.ca.gov/resources/documents/toxic-air-contaminant-identification-reports">https://ww2.arb.ca.gov/resources/documents/toxic-air-contaminant-identification-reports</a><br><br><a href="https://www.cdpr.ca.gov/docs/legbills/calcode/040201.htm#a6860">https://www.cdpr.ca.gov/docs/legbills/calcode/040201.htm#a6860</a> |
| Colorado    | Colorado Department of Public Health and Environment                                          | <a href="https://cdphe.colorado.gov/air-toxics">https://cdphe.colorado.gov/air-toxics</a><br><br><a href="https://cdphe.colorado.gov/toxic-air-contaminant-list">https://cdphe.colorado.gov/toxic-air-contaminant-list</a>                                                                                                                                                                                                                                                                                                                                                |
| Connecticut | Department of Energy and Environmental Protection                                             | <a href="https://portal.ct.gov/DEEP/Air/Planning/Toxics/Air-Toxics---Background-Information">https://portal.ct.gov/DEEP/Air/Planning/Toxics/Air-Toxics---Background-Information</a>                                                                                                                                                                                                                                                                                                                                                                                       |
| Delaware    | Department of Natural Resources and Environmental Control / Division of Air Quality           | <a href="https://dnrec.delaware.gov/air/quality/air-toxics/#:~:text=Gaseous%20air%20toxic%20pollutants%20include,a%20solvent%20by%20various%20industries.">https://dnrec.delaware.gov/air/quality/air-toxics/#:~:text=Gaseous%20air%20toxic%20pollutants%20include,a%20solvent%20by%20various%20industries.</a>                                                                                                                                                                                                                                                           |
| Florida     | Department of Environmental Protection/ Division of Air Resources Management                  | <a href="https://floridadep.gov/Air">https://floridadep.gov/Air</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|               |                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Georgia       | Georgia Environmental Protection Division                                                                    | <a href="https://epd.georgia.gov/air-protection-branch-technical-guidance-0/toxic-impact-assessment-guideline">https://epd.georgia.gov/air-protection-branch-technical-guidance-0/toxic-impact-assessment-guideline</a><br><a href="https://epd.georgia.gov/document/document/appendix-list-tap-aac-and-mer/download">https://epd.georgia.gov/document/document/appendix-list-tap-aac-and-mer/download</a> |
| Hawaii        | Hawaii Department of Health / Clean Air Branch                                                               | <a href="https://health.hawaii.gov/cab/">https://health.hawaii.gov/cab/</a>                                                                                                                                                                                                                                                                                                                                |
| Idaho         | Idaho Department of Environmental Quality                                                                    | <a href="https://www.deq.idaho.gov/air-quality/">https://www.deq.idaho.gov/air-quality/</a>                                                                                                                                                                                                                                                                                                                |
| Illinois      | Illinois Pollution Control Board                                                                             | <a href="https://pcb.illinois.gov/">https://pcb.illinois.gov/</a>                                                                                                                                                                                                                                                                                                                                          |
| Indiana       | Indiana Department of Environmental Management / Air Toxics Program                                          | <a href="https://www.in.gov/idem/toxic/">https://www.in.gov/idem/toxic/</a>                                                                                                                                                                                                                                                                                                                                |
| Iowa          | Iowa Department of Natural Resources                                                                         | <a href="https://www.iowadnr.gov/environmental-protection/air-quality/air-pollutants">https://www.iowadnr.gov/environmental-protection/air-quality/air-pollutants</a>                                                                                                                                                                                                                                      |
| Kansas        | Department of Health and Environment / Division of Environment                                               | <a href="https://www.kdhe.ks.gov/166/Air">https://www.kdhe.ks.gov/166/Air</a>                                                                                                                                                                                                                                                                                                                              |
| Kentucky      | Kentucky Energy and Environment Cabinet                                                                      | <a href="https://eec.ky.gov/Environmental-Protection/Air/Pages/Air-Quality-Regulations.aspx">https://eec.ky.gov/Environmental-Protection/Air/Pages/Air-Quality-Regulations.aspx</a>                                                                                                                                                                                                                        |
| Louisiana     | Louisiana Department of Environmental Quality                                                                | <a href="https://deq.louisiana.gov/faq/category/19">https://deq.louisiana.gov/faq/category/19</a>                                                                                                                                                                                                                                                                                                          |
| Maine         | Maine Department of Environmental Protection                                                                 | <a href="https://www.maine.gov/dep/air/monitoring/index.html">https://www.maine.gov/dep/air/monitoring/index.html</a>                                                                                                                                                                                                                                                                                      |
| Maryland      | Maryland Department of the Environment                                                                       | <a href="https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx">https://mde.maryland.gov/programs/permits/airmanagementpermits/pages/toxicairpollutantregulationdocuments.aspx</a>                                                                                                                                                                |
| Massachusetts | Massachusetts Department of Environmental Protection                                                         | <a href="https://www.mass.gov/info-details/massdep-ambient-air-toxics-guidelines">https://www.mass.gov/info-details/massdep-ambient-air-toxics-guidelines</a>                                                                                                                                                                                                                                              |
| Michigan      | Department of Environment, Great Lakes, and Energy                                                           | <a href="https://www.michigan.gov/egle/about/organization/air-quality/air-toxics">https://www.michigan.gov/egle/about/organization/air-quality/air-toxics</a>                                                                                                                                                                                                                                              |
| Minnesota     | Minnesota Pollution Control Agency / Minnesota Department of Health                                          | <a href="https://www.pca.state.mn.us/business-with-us/pollutant-categories-for-air-toxics">https://www.pca.state.mn.us/business-with-us/pollutant-categories-for-air-toxics</a><br><a href="https://www.health.state.mn.us/communities/environment/risk/guidance/air/table.html">https://www.health.state.mn.us/communities/environment/risk/guidance/air/table.html</a>                                   |
| Mississippi   | Mississippi Department of Environmental Quality                                                              | <a href="https://www.mdeq.ms.gov/air/air-emissions-standards/national-emission-standards-for-hazardous-air-pollutants/">https://www.mdeq.ms.gov/air/air-emissions-standards/national-emission-standards-for-hazardous-air-pollutants/</a>                                                                                                                                                                  |
| Missouri      | Missouri Department of Natural Resources / Division of Environmental Quality / Air Pollution Control Program | <a href="https://dnr.mo.gov/air/how-s-air/pollutants-sources/hazardous-air-pollutants-haps">https://dnr.mo.gov/air/how-s-air/pollutants-sources/hazardous-air-pollutants-haps</a><br><a href="https://dnr.mo.gov/document-search/table-">https://dnr.mo.gov/document-search/table-</a>                                                                                                                     |

|                |                                                                        |                                                                                                                                                                                                                                                                                                                                                   |
|----------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                |                                                                        | <a href="#">hazardous-air-pollutants-screening-model-action-levels-risk-assessment-levels</a>                                                                                                                                                                                                                                                     |
| Montana        | Montana Department of Environmental Quality                            | <a href="https://deq.mt.gov/air/index">https://deq.mt.gov/air/index</a>                                                                                                                                                                                                                                                                           |
| Nebraska       | Nebraska Department of Environment and Energy                          | <a href="http://dee.ne.gov/NDEQProg.nsf/OnWeb/AirToxics">http://dee.ne.gov/NDEQProg.nsf/OnWeb/AirToxics</a>                                                                                                                                                                                                                                       |
| Nevada         | Nevada Division of Environmental Protection                            | <a href="https://ndep.nv.gov/air/air-pollutants">https://ndep.nv.gov/air/air-pollutants</a>                                                                                                                                                                                                                                                       |
| New Hampshire  | New Hampshire Department of Environmental Services                     | <a href="https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance">https://www.des.nh.gov/air/industrial-sources/air-toxics-compliance</a>                                                                                                                                                                                             |
| New Jersey     | New Jersey Department of Environmental Protection                      | <a href="https://dep.nj.gov/airplanning/airtoxics/">https://dep.nj.gov/airplanning/airtoxics/</a><br><br>PFOA and PFOS: <a href="https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf">https://dep.nj.gov/wp-content/uploads/dsr/njdep-pfoa-pfos-rfc-memo.pdf</a>                                                               |
| New Mexico     | New Mexico Environment Department                                      | <a href="https://www.env.nm.gov/air-quality/">https://www.env.nm.gov/air-quality/</a>                                                                                                                                                                                                                                                             |
| New York       | New York Department of Environmental Conservation / Air Toxics Program | <a href="https://dec.ny.gov/environmental-protection/air-quality/controlling-pollution-from-facilities/air-toxics-program">https://dec.ny.gov/environmental-protection/air-quality/controlling-pollution-from-facilities/air-toxics-program</a>                                                                                                   |
| North Carolina | North Carolina Department of Environmental Quality                     | <a href="https://www.deq.nc.gov/about/divisions/air-quality/air-quality-planning/air-quality-rules-regulations/hazardous-air-pollutants-and-toxic-air-pollutants-haps-taps">https://www.deq.nc.gov/about/divisions/air-quality/air-quality-planning/air-quality-rules-regulations/hazardous-air-pollutants-and-toxic-air-pollutants-haps-taps</a> |
| North Dakota   | North Dakota Department of Environmental Quality                       | <a href="https://deq.nd.gov/aq/permitting/HAPs.aspx">https://deq.nd.gov/aq/permitting/HAPs.aspx</a>                                                                                                                                                                                                                                               |
| Ohio           | Ohio Environmental Protection Agency                                   | <a href="https://epa.ohio.gov/divisions-and-offices/air-pollution-control/reports-and-data/air-toxics">https://epa.ohio.gov/divisions-and-offices/air-pollution-control/reports-and-data/air-toxics</a>                                                                                                                                           |
| Oklahoma       | Oklahoma Department of Environmental Quality                           | <a href="https://www.deq.ok.gov/air-quality-division/emissions-inventory/oklahoma-regulated-air-pollutants/">https://www.deq.ok.gov/air-quality-division/emissions-inventory/oklahoma-regulated-air-pollutants/</a>                                                                                                                               |
| Pennsylvania   | Pennsylvania Department of Environmental Protection                    | <a href="https://www.dep.pa.gov/Business/Air/BAQ/MonitoringTopics/ToxicPollutants/pages/default.aspx">https://www.dep.pa.gov/Business/Air/BAQ/MonitoringTopics/ToxicPollutants/pages/default.aspx</a>                                                                                                                                             |
| Rhode Island   | Rhode Island Department of Environmental Management                    | <a href="https://dem.ri.gov/environmental-protection-bureau/air-resources/air-monitoring">https://dem.ri.gov/environmental-protection-bureau/air-resources/air-monitoring</a>                                                                                                                                                                     |
| South Carolina | South Carolina Department of Health and Environmental Control          | <a href="https://scdhec.gov/environment/air-quality/compliance-monitoring/hazardous-air-pollutants-reporting-standards-major">https://scdhec.gov/environment/air-quality/compliance-monitoring/hazardous-air-pollutants-reporting-standards-major</a>                                                                                             |
| South Dakota   | South Dakota Department of Agriculture and Natural Resources           | <a href="https://danr.sd.gov/Environment/AirQuality/PermitForms/default.aspx">https://danr.sd.gov/Environment/AirQuality/PermitForms/default.aspx</a>                                                                                                                                                                                             |
| Tennessee      | Tennessee Department of Environment and Conservation                   | <a href="https://www.tn.gov/environment/air.html">https://www.tn.gov/environment/air.html</a>                                                                                                                                                                                                                                                     |
| Texas          | Texas Commission on Environmental Quality                              | <a href="https://www.tceq.texas.gov/toxicology/index.html">https://www.tceq.texas.gov/toxicology/index.html</a>                                                                                                                                                                                                                                   |

|                                    |                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Utah                               | Utah Department of Environmental Quality                                                | <a href="https://deq.utah.gov/air-quality/macts-and-other-neshaps-air-toxics-lead-and-asbestos-section-atlas">https://deq.utah.gov/air-quality/macts-and-other-neshaps-air-toxics-lead-and-asbestos-section-atlas</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Vermont                            | Vermont Department of Environmental Conservation                                        | <a href="https://dec.vermont.gov/air-quality/pollutants-health/haz-air-contaminants">https://dec.vermont.gov/air-quality/pollutants-health/haz-air-contaminants</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Virginia                           | Virginia Department of Environmental Quality                                            | <a href="https://www.deq.virginia.gov/our-programs/air/monitoring-assessments/air-monitoring/pollutant-monitoring">https://www.deq.virginia.gov/our-programs/air/monitoring-assessments/air-monitoring/pollutant-monitoring</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Washington                         | Washington Department of Ecology                                                        | <a href="https://ecology.wa.gov/Air-Climate/Air-quality/Air-quality-targets/Air-quality-standards#:~:text=Lead%20(Pb),Particle%20or%20particulate%20matter%20(PM)">https://ecology.wa.gov/Air-Climate/Air-quality/Air-quality-targets/Air-quality-standards#:~:text=Lead%20(Pb),Particle%20or%20particulate%20matter%20(PM)</a>                                                                                                                                                                                                                                                                                                                                                        |
| West Virginia                      | West Virginia Department of Environmental Protection                                    | <a href="https://dep.wv.gov/daq/small%20business/Pages/HazardousAirPollutants.aspx">https://dep.wv.gov/daq/small%20business/Pages/HazardousAirPollutants.aspx</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Wisconsin                          | Wisconsin Department of Natural Resources                                               | <a href="https://dnr.wisconsin.gov/topic/AirQuality/Rules.html">https://dnr.wisconsin.gov/topic/AirQuality/Rules.html</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Wyoming                            | Wyoming Department of Environmental Quality                                             | <a href="https://deq.wyoming.gov/aqd/">https://deq.wyoming.gov/aqd/</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>International Organizations</b> |                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Australia                          | Australian Government / Department of Climate Change, Energy, the Environment and Water | <a href="https://www.dcceew.gov.au/environment/protection/air-quality/air-pollutants">https://www.dcceew.gov.au/environment/protection/air-quality/air-pollutants</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Canada                             | Government of Canada / Environment and Natural Resources                                | <a href="https://www.canada.ca/en/environment-climate-change/services/air-pollution/pollutants/toxic.html">https://www.canada.ca/en/environment-climate-change/services/air-pollution/pollutants/toxic.html</a><br><a href="https://www.canada.ca/en/environment-climate-change/services/management-toxic-substances/list-canadian-environmental-protection-act.html">https://www.canada.ca/en/environment-climate-change/services/management-toxic-substances/list-canadian-environmental-protection-act.html</a>                                                                                                                                                                     |
| European Union                     | European Environment Agency / European Chemicals Agency                                 | <a href="https://www.eea.europa.eu/en/topics/in-depth/air-pollution?activeAccordion=">https://www.eea.europa.eu/en/topics/in-depth/air-pollution?activeAccordion=</a><br><a href="https://environment.ec.europa.eu/topics/air/air-quality/eu-air-quality-standards_en">https://environment.ec.europa.eu/topics/air/air-quality/eu-air-quality-standards_en</a><br><a href="https://echa.europa.eu/air-annexes-2008-50?p_p_id=eucleflegislationlist_WAR_euclefportlet&amp;p_p_lifecycle=0">https://echa.europa.eu/air-annexes-2008-50?p_p_id=eucleflegislationlist_WAR_euclefportlet&amp;p_p_lifecycle=0</a><br><a href="https://chem.echa.europa.eu/">https://chem.echa.europa.eu/</a> |
| World Health Organization          | Air quality, energy and health                                                          | <a href="https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/health-impacts/types-of-pollutants">https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/health-impacts/types-of-pollutants</a>                                                                                                                                                                                                                                                                                                                                                                                                                      |

## **Appendix M: Background on Uncertainty Factors Used in Oregon**

# Appendix M: Background on Uncertainty Factors used in Oregon

## Section 1 General guidance and resources

### 1.1 Introduction, adapted from Minnesota Department of Health's Air Guidance Values Technical Support Document (MDH 2025)

To account for what is not known about a chemical's toxicity to a human population, uncertainty factors (UF) are applied when deriving a noncancer TRV. Once the dose level (e.g., NOAEL, LOAEL or BMCL) has been selected as the POD, it is then divided by uncertainty factors to derive the TRV. OHA considers the application of five UFs:

- Interspecies extrapolation ( $UF_A$ )
- Intraspecies variability ( $UF_H$ )
- LOAEL to NOAEL extrapolation ( $UF_L$ )
- Subchronic-to-chronic extrapolation ( $UF_S$ )
- Database uncertainty ( $UF_D$ )

In the absence of chemical-specific information, each of the five factors is typically assigned a value between 1 and 10. UFs are normally expressed as full or half powers of ten, such as  $10^0$  (=1),  $10^{0.5}$  (=3.16), and  $10^1$  (=10). All applicable UFs are multiplied together to yield a composite UF for the air guidance value. Half power values such as  $10^{0.5}$  are factored as whole numbers when they occur singly but as powers or logs when they occur in tandem (EPA 2002). Therefore, a composite UF using values of 3 and 10 would be expressed as 30 ( $3 \times 10^1$ ), whereas a composite UF using values of 3 and 3 would be expressed as 10 ( $10^{0.5} \times 10^{0.5} = 10^1$ ). The maximum total UF used to derive an inhalation TRV in Oregon is 3,000 (Chapter 2 of the TRV Support Document). If the uncertainty associated with a chemical's toxicity warrants application of UFs where the product exceeds 3,000, OHA believes there is insufficient chemical information to derive a value.

### 1.2 Reference materials OHA refers to when evaluating UFs

There is some variety in how different agencies handle scientific uncertainty and apply UFs. OHA generally tries to follow the guidance used by DEQ's authoritative sources (EPA, ATSDR, and CalEPA). Each agency has developed resources describing their UF practices:

## **EPA Guidance Document**

- Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry, US EPA, October 1994, available at: <https://www.epa.gov/risk/methods-derivation-inhalation-reference-concentrations-and-application-inhalation-dosimetry> (especially Table 4-9) (EPA 1994)

## **ATSDR Guidance Documents**

- Pohl, H.R., Abadin, H.G. (1995) Utilizing Uncertainty Factors in Minimal Risk Levels Derivation. *Regulatory Toxicology and Pharmacology* (**22**), 180-188, available at: <https://pubmed.ncbi.nlm.nih.gov/8577953/> (Pohl and Abadin 1995)
- Przybyla, J., Buser, M.C., Abadin, H.G., Pohl, H.R., (2020) Evaluation of ATSDR's MRL and EPA's RfCs/RfDs: Similarities, Differences, and Rationales. *Journal of Toxicological Pharmacology* (**4**)(1): 1-13, available at: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10300620/> (Przybyla et al. 2020)

## **CalEPA Guidance Document**

- OEHHA (2008) Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Oakland, CA, available at: <https://oehha.ca.gov/sites/default/files/media/downloads/crnrr/noncancertsdfinal.pdf> (OEHHA 2008)

## **Section 2 Specific information on UF categories**

This section lists specific categories of UFs and OHA's policies on default values for each category. OHA records each UF applied for each candidate TRV in Workbook 2: TRV Derivations.

When a TRV candidate comes from EPA, ATSDR, or CalEPA, OHA's policy is to adopt the UFs applied by the originating agency. In cases where OHA has to select a candidate TRV from an alternate source, OHA may modify UFs to conform with the following policies informed by the above referenced guidance from EPA, ATSDR, and CalEPA and summarized below.

When OHA modified UFs for a TRV, OHA listed "DEQ in consultation with ATSAC" as the authoritative source in Workbook 1 and Workbook 2. Chapter 5 in the TRV Support Document describes details on any adjustments to UFs made for any TRV where DEQ in consultation with ATSAC is listed as the authoritative source. In cases where OHA modified UFs, staff followed the general policies below, which are generally consistent with those of the EPA, ATSDR, and CalEPA.



## 2.1 Interspecies uncertainty factor ( $UF_A$ )

A  $UF_A$  is used to account for the uncertainty in extrapolating laboratory animal data to humans (EPA 1994). When the POD is set based on a study in humans, OHA assigns a value of 1 for  $UF_A$  because there is no interspecies extrapolation in this case. When the POD is set based on a study in most non-human animals (e.g., rats and mice), OHA assigns a value of 10 for  $UF_A$  unless the source agency has applied an interspecies dosimetric adjustment to the POD to create a human equivalent concentration ( $POD_{HEC}$ ) to quantitatively account for toxicokinetic differences between the test species and humans. If starting from a  $POD_{HEC}$ , OHA assigns a  $UF_A$  of 3 to account for the potential remaining toxicodynamic differences between the test species and humans. If the test species underlying a POD is a non-human primate, OHA assigns a  $UF_A$  of 3 because of the anatomical and physiological similarities between humans and non-human primates.

## 2.2 Intraspecies uncertainty factor ( $UF_H$ )

A  $UF_H$  is used to account for the variation in sensitivity among members of the human population (EPA 1994). OHA assigns a  $UF_H$  of 10 unless the critical study underlying the POD is in humans and included sensitive populations like young children or people with pre-existing conditions such as asthma. If the POD is based on a human study that included sensitive groups, OHA may reduce the  $UF_H$  to 3.

## 2.3 LOAEL to NOAEL uncertainty factor ( $UF_L$ )

A  $UF_L$  is used to account for the uncertainty in using lowest observed adverse effect level (LOAEL) data rather than no observed adverse effect level (NOAEL) data for the POD (EPA 1994). OHA's policy on default values for  $UF_L$  depends on the type of POD the candidate TRV is based on. If the POD is a BMCL or NOAEL, the default value for  $UF_L$  is 1 because there is much less uncertainty about the concentration that did not cause harm in the critical study. When the POD is a LOAEL, there is uncertainty about what concentration would have resulted in no observable adverse effect. OHA's policy on the default value for  $UF_L$  when the POD is a LOAEL is 10. Like ATSDR and CalEPA, OHA may reduce the  $UF_L$  if there is reliable information that the observed effect was mild/minor, reversible, or very near a probable NOAEL. OHA will not reduce the  $UF_L$  to less than 3 when the POD is a LOAEL.

## 2.4 Subchronic uncertainty factor ( $UF_S$ )

A  $UF_S$  is only applicable to chronic TRVs. This is because they are applied to account for uncertainty from extrapolating subchronic exposure durations (exposures lasting less than 12% of the average lifespan of the test species) in critical studies to chronic TRVs (EPA 1994). Therefore, OHA's policy default value for  $UF_S$  for acute TRVs is 1.

When calculating a chronic TRV based on a subchronic POD, OHA considers the factors recommended by EPA (EPA 1994):

- Does the damage caused in the critical study accumulate with time? If yes, this indicates the need for a larger  $UF_s$ .
- Is the damage caused in the critical study more dependent on concentration than time? If yes, this indicates that a lower  $UF_s$  may be acceptable.
- What was the exposure duration in the critical study (see guidance from CalEPA to evaluate)?

Expanding the duration of exposure consideration, OHA's policy is to follow CalEPA's guidance when assigning a  $UF_s$  (OEHHA 2008):

- Exposures less than 8% of the test species' lifetime should get a  $UF_s$  of 10.
- Exposures from 8-12% of the test species' lifetime should get a  $UF_s$  of 3.
- Exposures equal to or greater than 12% of the test species' lifetime should get a  $UF_s$  of 1.

CalEPA's 2008 guidance includes a useful table (Table 7.2.1) that shows average lifespans of common test species to calculate percentages (OEHHA 2008). OHA agrees with EPA's rule that a 13-week study in rodents counts as between 8 and 12% of the test species' lifetime and qualifies for a  $UF_s$  of 3 in most cases. However, if there is evidence of potential for cumulative damage, such as effects seen with exposures longer than 13 weeks by another exposure route that were not seen at 13 weeks by the same route of exposure, a larger  $UF_s$  may be warranted.

## 2.5 Database uncertainty factor ( $UF_D$ )

A  $UF_D$  is used to account for the inability of a single study (or two) to adequately address all possible adverse human health outcomes (EPA 1994). This UF is about the level of confidence that the range of available studies includes a quality evaluation of the health effect that occurs at the lowest concentration for a given TAC (i.e. the most sensitive critical effect). For well-studied TACs with many studies, testing a comprehensive set of potential health effects and organ systems, a  $UF_D$  of 1 is often appropriate. When very few studies are available and only a limited number of potential health effects have been evaluated, OHA prefers  $UF_D$  of 10. If most health effects have been evaluated except for one important category, then OHA may apply a  $UF_D$  of 3. An example of this might be a TAC where many studies are available evaluating many health effects, but there are no developmental toxicity studies available. The quality of available studies may also factor into selection of the  $UF_D$  value.

This uncertainty factor requires case-by-case evaluation and professional judgement.

### Section 3 Variability across agencies

Uncertainty is inherent in deriving TRVs and strategies for quantifying uncertainty differ between toxicologists as well as organizations that set TRVs. Therefore, when comparing TRVs for the same TAC and risk category across different source agencies, it is common to see a range of UF values depending on agency policies.

Table M-1 shows the range of UF guidelines from across different agencies including OHA's preferred defaults. As stated earlier, OHA prefers to defer to the UFs applied by EPA, ATSDR, and CalEPA when they are the source of the candidate TRV. In cases where OHA needs to seek TRVs from alternate sources, OHA will follow policies in the "OHA" column of Table M-1 below and described in the previous section of this appendix and in Chapter 2.

**Table M-1.** Adapted from Table 3-6 from the TCEQ Guidelines to Develop Toxicity Factors (pg. 91), which is a comparison of UFs used by different organizations (TCEQ 2015)

| Uncertainty Factors                    | TCEQ                                                                               | EPA  | ATSDR                                     | CalEPA (OEHHA)                        | OHA                                       |
|----------------------------------------|------------------------------------------------------------------------------------|------|-------------------------------------------|---------------------------------------|-------------------------------------------|
| Intraspecies, UF <sub>A</sub>          | ≤ 10                                                                               | ≤ 10 | 1, 3, or 10                               | ≤ 10                                  | 1, 3, or 10                               |
| Interspecies, UF <sub>H</sub>          | ≤ 10                                                                               | ≤ 10 | 1, 3, or 10                               | ≤ 100                                 | 1, 3, or 10                               |
| LOAEL to NOAEL, UF <sub>L</sub>        | 2 – 3 (≤ mild), 6 (mild/severe), 10 (severe)                                       | ≤ 10 | 3 (minimal effects), 10 (serious effects) | 6 (mild effects), 10 (severe effects) | 3 (minimal effects), 10 (serious effects) |
| Subchronic to chronic, UF <sub>S</sub> | ≤ 10                                                                               | ≤ 10 | 1, 3, or 10                               | 1, 3, or 10                           | 1, 3, or 10                               |
| Incomplete database, UF <sub>D</sub>   | ≤ 10 =database deficiency and key study quality, including child/adult differences | ≤ 10 | N/A                                       | 1 or 3                                | 1, 3, or 10                               |

Blue shading indicates authoritative sources of TRVs listed in DEQ rule (OAR 340-247-0030); Yellow shading indicates OHA preferred defaults in cases where a candidate TRV is coming from an alternate source.

### Section 4 References

EPA. 1994. "Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry." U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment,

- Washington, DC, EPA/600/8-90/066F.  
<https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993>.
- EPA. 2002. *A Review of the Reference Dose and Reference Concentration Processes (Final 2002)*. U.S. Environmental Protection Agency (EPA), Risk Assessment Forum, EPA/630/P-02/002F. <https://www.epa.gov/sites/default/files/2014-12/documents/rfd-final.pdf>.
- MDH. 2025. *Air Guidance Values Technical Support Document*. Minnesota Department of Health (MDH).  
<https://www.health.state.mn.us/communities/environment/air/docs/airguidancetech.pdf>.
- OEHHA. 2008. *Technical Support Document for the Derivation of Noncancer Reference Exposure Levels*. Office of Environmental Health Hazard Assessment (OEHHA), Air Toxics Hot Spots.  
<https://oehha.ca.gov/sites/default/files/media/downloads/crnrr/noncancertsdfinal.pdf>.
- Pohl, Hana R, and Henry G Abadin. 1995. "Utilizing Uncertainty Factors in Minimal Risk Levels Derivation." *Regulatory Toxicology and Pharmacology* 22 (2): 180–88.
- Przybyla, Jennifer, Melanie C Buser, Henry G Abadin, and Hana R Pohl. 2020. "Evaluation of ATSDR's MRL and EPA's RfCs/RfDs: Similarities, Differences, and Rationales." *Journal of Toxicology and Pharmacology* 4 (1): 1.
- TCEQ. 2015. "TCEQ Guidelines to Develop Toxicity Factors." RG-442: Toxicology Division of the Texas Commission on Environmental Quality (TCEQ), September.  
<https://www.tceq.texas.gov/downloads/toxicology/publications/rg-442.pdf>.

## **Appendix N: Manganese Petition**

November 1, 2022

## **Supporting Evidence for Petition for Oregon Department of Environmental Quality (ODEQ) Air Toxics Review to Revise the Acute Toxicity Reference Value (TRV) for Acute Manganese Exposure**

A petition has been submitted to the Oregon Department of Environmental Quality (ODEQ) to propose an alternative short-term guideline concentration (SGC) and toxicity reference value (TRV) for acute (24-hour) exposure to manganese, as provided in Oregon Administrative Rule (OAR) 340-247-0040(4). This document provides the supporting scientific evidence for a revised SGC and acute TRV of  $5 \mu\text{g}/\text{m}^3$ . As described below, the evidence supporting an updated SGC and TRV for acute manganese includes the following: authoritative source information; inhalation toxicity reference values established by another state; publicly available and peer-reviewed toxicity testing data; and a peer-reviewed, published physiologically based pharmacokinetic (PBPK) model.

### **1 The basis for ODEQ's current toxicity reference value (TRV) and short-term guideline concentration (SGC) for acute manganese exposure are not consistent with current authoritative sources, are based on long-term exposure study data, and are not current with the scientific literature.**

ODEQ's acute toxicity reference value (TRV) for manganese ( $0.3 \mu\text{g}/\text{m}^3$ )<sup>1</sup> is applied to exposures up to 24 hours. This TRV was set at the same value as the short-term guideline concentration (SGC) developed by ODEQ and the Oregon Health Authority (OHA).<sup>2</sup> (For simplicity, we will reference only the TRV in our discussion, but the same comments apply to the SGC.) ODEQ's TRV is not set by reference to acute exposure information. Instead, the TRV is based on a long-term exposure guideline (chronic reference exposure level [REL]) published in 2008 by California's Office of Environmental Health Hazard Assessment (OEHHA, 2008b). Although ODEQ air toxics regulations list CalEPA (and thus OEHHA) as an authoritative source from which information can be used to identify TRVs, OEHHA did not set an acute exposure guideline. Moreover, use of a chronic value like the guideline set by OEHHA in 2008 is in direct contrast to the OHA's recommendation that extrapolating from chronic values should be avoided and is to be considered only when the endpoint for the acute exposures is relevant to the chronic effect

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<sup>1</sup> Oregon Administrative Rules (OAR 340-247-8010).

<sup>2</sup> Oregon Health Authority. 2019. Short-term guideline concentrations for air toxics. October 29.

(OHA, 2019<sup>2</sup>). As described herein, ODEQ's prior decision to convert OEHHA's chronic REL to an acute value of ODEQ's creation by applying what equates to a chronic-to-acute uncertainty factor is not supported by any authoritative source or published science.

### 1.1 OEHHA's REL

OEHHA's 2008 REL is based on a study of neurotoxicity in workers exposed for an average of 5.3 years and up to 17 years (Roels et al., 1992). To derive an SGC from OEHHA's chronic REL, ODEQ multiplied the OEHHA REL ( $0.09 \mu\text{g}/\text{m}^3$ ) by an uncertainty factor equal to the square root of 10, to reverse OEHHA's adjustment from subchronic to chronic exposures when setting the REL. OEHHA applied a subchronic adjustment factor to the study results, because, in the underlying study, worker exposures were evaluated for an average exposure of 5.3 years, which is less than the 7 years that OEHHA uses for chronic exposures. Clearly, average exposures of 5.3 years and upper-bound exposures of 17 years in the study are not appropriate evaluation periods for acute 24-hour exposure. In fact, 5.3 years is very close to the chronic exposure timeframe of at least 7 years that would not require adjustment from subchronic to chronic (10% of a lifetime) (OEHHA, 2008a), and data from the Roels et al. (1992) study therefore were appropriate for direct application to evaluate chronic exposures. The same study, however, should not be used to evaluate acute, 24-hour exposures.

While OEHHA has developed acute RELs for some chemicals (to be applied to maximum hourly exposures), OEHHA did not develop an acute REL for manganese, because they did not judge the available data to be appropriate for short-term exposures. In fact, OEHHA specifically concluded that: "No studies of acute manganese inhalation were located that demonstrated a dose-response or evaluated other toxicological endpoints" (OEHHA, 2008b). Therefore, OEHHA did not establish an acute REL.

### 1.2 ATSDR's Minimal Risk Level

The Agency for Toxic Substance Disease Registry (ATSDR), also listed as an authoritative source in Oregon regulations, developed a chronic inhalation minimum risk level (MRL) for manganese of  $0.3 \mu\text{g}/\text{m}^3$  (ATSDR, 2012). It is important to note that the ATSDR assessment is more current than the OEHHA REL and relies on an enhanced investigation of the same occupational exposure data (Roels et al., 1992). The ATSDR chronic MRL is equal to the ODEQ acute TRV, demonstrating on its face that the acute TRV is unnecessarily conservative.

The ATSDR chronic MRL is based on the neurological endpoint of abnormal hand-eye coordination, as described in Roels et al. (1992). ATSDR calculated a benchmark concentration level for potential adverse effects in 10% of the population ( $\text{BMCL}_{10}$ ), as recommended by U.S. EPA (2012), using the individual-level data provided by the authors to calculate the point of departure (POD) of  $142 \mu\text{g}/\text{m}^3$ . Following adjustments for worker exposures ( $5/7 \text{ days/week} \times 8/24 \text{ hours per day} \times 142 \mu\text{g}/\text{m}^3 = 34 \mu\text{g}/\text{m}^3$ ), ATSDR applied uncertainty factors of 10 for human variability, citing the published PBPK models for demonstrating the lack of effect among neonates and young children, and 10 for

limitations/uncertainties in the database, including that the workers in the Roels et al. (1992) study were exposed to manganese oxide, which is an insoluble form of manganese that is expected to have lower bioavailability than soluble forms. Unlike OEHHA, ATSDR did not include a factor for extrapolating from subchronic to chronic exposure. These uncertainty factors result in the chronic MRL of  $0.3 \mu\text{g}/\text{m}^3$  [ $34 \mu\text{g}/\text{m}^3/(10 \times 10)$ ].

Similar to OEHHA, ATSDR did not develop an acute MRL, or even an intermediate MRL, stating that “The available data on the toxicity of inhaled manganese were considered inadequate for derivation of acute- or intermediate-duration inhalation MRLs” (ATSDR, 2012). In addition, ATSDR highlighted that respiratory effects were relevant to acute exposures. ATSDR summarized, “Several acute- and intermediate-duration studies in animals report various signs of lung inflammation following periods ranging from one day to ten months at manganese concentrations ranging from 0.7 to 69  $\text{mg}/\text{m}^3$ .” No-observed-adverse-effect levels (NOAELs) for respiratory effects from acute exposures reported by ATSDR (2012) range from approximately 2 to 14  $\text{mg}/\text{m}^3$ . ATSDR concluded that intermediate and acute MRLs based on animal data would be lower<sup>3</sup> than the chronic MRL, which was based on human data, and therefore, these shorter term MRLs were unnecessary.

### **1.3 Authoritative-Source Information for Chronic Exposure is not Appropriate for Setting an Acute TRV**

To summarize, ODEQ set its TRV by relying on OEHHA’s chronic values, which were based on a long-term occupational study wherein neurological effects were observed. As noted by ATSDR, although acute health effects on the respiratory system may result from acute inhalation exposure to manganese, neither the OEHHA REL nor the ATSDR MRL were developed from underlying data that represented short-term exposure or effects on the respiratory system. Both agencies, OEHHA and ATSDR, concluded that the data they reviewed were not sufficient to develop an acute exposure value. Given this conclusion from these authoritative sources, it is evident that ODEQ’s current TRV is not based on relevant toxicity information from one or more of the authoritative sources listed in OAR 340-247-0030 (i.e., none of the listed authoritative sources have set an acute TRV for manganese) and is inappropriate for continued use. The following section of this document details the evidence that supports revising ODEQ’s acute TRV for manganese.

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<sup>3</sup> The acute and intermediate MRLs would require additional uncertainty factors because they would be based on animal data, as compared to the chronic MRL based on human data. The ATSDR stated that it believed the chronic value is also adequately protective of acute and intermediate exposures.



## **2 ODEQ's acute TRV for Mn should be revised to include recent, more applicable regulatory and peer-reviewed, publicly available academic information relevant to acute exposures.**

Consistent with OAR 340-247-0040(4), ODEQ should revise its acute TRV for Mn, based on the information used to set acute TRVs for Mn in Texas (Section 2.1) and the most current, peer-reviewed toxicity information that is publicly available (Section 2.2).

### **2.1 Alternative Regulatory Acute TRVs for Setting an Updated TRV for Mn**

The Texas Commission on Environmental Quality (TCEQ) has developed a 24-hour Mn acute toxicity criterion based on short-term toxicity study data (TCEQ, 2017). Specifically, TCEQ<sup>4</sup> developed an air monitoring comparison value (AMCV)<sup>5</sup> for a 24-hour period of 5.0 µg/m<sup>3</sup>. “The Texas Commission on Environmental Quality's (TCEQ) Air Monitoring Comparison Values (AMCVs) are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. AMCVs are based on data concerning health effects, odor, and vegetation effects. They are not ambient air standards.” TCEQ conducts a thorough literature review to set its criteria.

TCEQ's 24-hour AMCV is based on the non-human primate (NHP) study reporting respiratory effects following exposures to manganese sulfate (MnSO<sub>4</sub>) by Dorman et al. (2005) (Attachment A).<sup>6</sup> The TCEQ 24-hr AMCV is conservative, because it is based on mild, and transient, respiratory effects observed following exposure to 1,500 µg Mn/m<sup>3</sup> for 6 hours per day, 5 days per week, for 3 weeks, which is 15 exposure days or 90 total hours of exposure (Dorman et al., 2005).<sup>7</sup> TCEQ applied an uncertainty factor of 300, to arrive at the 24-hour AMCV of 5.0 µg/m<sup>3</sup>.<sup>8</sup>

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<sup>4</sup> The Toxicology, Risk Assessment, and Research Division of TCEQ developed the inhalation AMCV. Similar to OEHHA's role in California, this division “helps TCEQ make scientifically sound decisions by applying toxicological principles when evaluating environmental data, issuing authorizations, developing environmental regulations and making policy decisions. TCEQ toxicologists identify chemical hazards, evaluate potential exposures, assess human health risks and communicate risk to the general public and stakeholders.” [TCEQ Toxicology - Texas Commission on Environmental Quality - www.tceq.texas.gov](http://www.tceq.texas.gov)

<sup>5</sup> [Air Monitoring Comparison Values \(texas.gov\)](http://www.tceq.texas.gov).

<sup>6</sup> Dorman et al. (2005) was reviewed by OEHHA and ATSDR, but was not used to set acute or intermediate MRLs as noted in Footnote 3. OEHHA's acute values are for 1-hr exposures, and the Dorman study was for much longer exposure durations. ATSDR's acute values are for 14 days. ATSDR could have used Dorman et al. (2005), but after adding uncertainty factors appropriate for 14 day exposures (rather than 24-hour exposures), the acute MRL would be lower than the chronic MRL. Using Dorman et al. (2005) for a 24-hour exposure point of departure (POD), as was done by TCEQ, is conservative and appropriate.

<sup>7</sup> Detailed summary of Dorman et al. (2005) is provided herein in Attachment B.

<sup>8</sup>  $\text{AMCV for Mn} \left( 5 \frac{\mu\text{g}}{\text{m}^3} \right) = 1.5 \frac{\text{mg}}{\text{m}^3} \times 1000 \frac{\mu\text{g}}{\text{mg}} \div 300$

The short-term inhalation toxicity guideline concentrations published by ODEQ and TCEQ are compared in Table 1.

**Table 1. Acute inhalation guidelines used by ODEQ and TCEQ**

| Agency | Name of Value                                                                                                                                 | Basis                                                                                                     | Value (µg/m <sup>3</sup> ) | Exposure Term |
|--------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|----------------------------|---------------|
| ODEQ   | Cleaner Air Oregon Program Short-Term Guideline Concentration/ Acute Noncancer toxicity reference value (TRV)/ risk-based concentration (RBC) | OEHHA chronic REL Neurological effects observed in workers (Roels et al. 1992); average exposed 5.3 years | 0.3                        | 24-hr         |
| TCEQ   | Short-term air monitoring comparison value (AMCV) <sup>1</sup>                                                                                | Mild transient effects in NHPs exposed for 90 hrs over 3 weeks (Dorman et al., 2005)                      | 9.1                        | 1-hr          |
|        | 24-hour air monitoring comparison value (AMCV)                                                                                                |                                                                                                           | 5.0                        | 24-hr         |

Abbreviations: µg/m<sup>3</sup> (microgram per cubic meter); hr (hour)

## 2.2 Current, Peer-Reviewed Short-Term Toxicity Data for Setting an Updated TRV for Mn

We conducted a current literature and regulatory review to identify the most relevant peer-reviewed toxicology and/or epidemiology data that could be used to set an updated acute TRV for manganese. The review included studies cited in existing regulatory guideline documents developed by TCEQ, ATSDR, and OEHHA to identify points of departure (PODs) (e.g., LOAELs, NOAELs, or benchmark doses [BMD]) for acute exposures. Next, we searched recent publications (since 2005) for relevant inhalation toxicity studies. In April of 2022, we performed a PubMed search for publications from 2005 to 2022 for “manganese inhalation toxicity.” The titles and abstracts of the results were mined for newer studies that could help inform a 24-hour inhalation exposure guideline. Of the peer-reviewed articles identified in the initial search, several animal studies were identified as being potentially relevant for developing a short-term inhalation value based on a review of the titles and abstracts. No epidemiology studies were identified. Although the papers were informative, none provide a POD that was lower than that from Dorman et al. (2005). The potentially relevant papers are summarized in Attachment B.

Overall, considering these papers, we concur with the TCEQ’s determination that, although exposures were short-term in nature but more than 24 hours, the data set from Dorman et al. (2005) provides the most appropriate POD for an acute TRV. The POD is the LOAEL of 1.5 mg Mn/m<sup>3</sup>. As explained in Dorman et al. (2005) (Attachment A), no dosimetric adjustment is required when using these data to assess exposures in humans. Use of the Dorman et al. (2005) LOAEL addresses one of the data gaps identified by ATSDR when it set the chronic MRL in 2012, because exposures in this study were to soluble manganese sulfate (MnSO<sub>4</sub>), which is bioavailable compared to the form (MnO<sub>2</sub>) in Roels et al. (1992) (Chen et al. 2015; Dorman et al. 2005). Further, the reproductive and developmental

toxicity study by McGough and Jardine (2017) addresses the uncertainty associated with selecting the Dorman et al. (2005) POD based on respiratory effects ( $1.5 \text{ mg Mn/m}^3$ ), because subchronic exposures in rats at higher levels (up to  $8.1 \text{ mg/m}^3$  for up to 714 hours) did not result in reproductive or developmental toxicity.

Although the potential for neurotoxicity from acute exposures seems unlikely, there is uncertainty regarding the potential for neurotoxicity based on the studies reviewed (Attachment B). To address this uncertainty, we cite and apply the currently published PBPK models (Schroeter et al. 2011; Yoon et al. 2019), which consider sensitive human life stages, to assess the potential for neurotoxicity from acute 24-hour exposures at the proposed TRV ( $5 \text{ } \mu\text{g/m}^3$ ) (Section 3). It is noteworthy that the data set from the Dorman et al. (2005) study was also used to parametrize the current PBPK models. Finally, Dorman et al. (2006) reported no neurological effects at any dose in the NHPs used in the 2005 study, based on veterinarian observations.

### **3 The proposed acute TRV/SGC of $5 \text{ } \mu\text{g/m}^3$ is associated with respiratory effects, consistent with the TCEQ AMCV, and would not result in potential neurotoxic effects, based on physiologically based pharmacokinetic (PBPK) modeling of manganese in the target tissue of the brain.**

#### **3.1 Proposed Acute TRV Based on Dorman et al. (2005)**

It is proposed that ODEQ set an updated acute SGC and TRV for manganese of  $5 \text{ } \mu\text{g/m}^3$ . This value is consistent with the 24-hour AMCV developed by TCEQ (2017).

The TCEQ Development Support Document (2017) included a detailed literature review when establishing its toxicity criteria. The Dorman et al. (2005) study evaluated several exposure profiles, including exposure of NHPs to  $1,500 \text{ } \mu\text{g/m}^3$  ( $1.5 \text{ mg/m}^3$ ) for 6 hours per day, 5 days/week, for 3 weeks (15 total exposure events). Dorman et al. (2005) also administered manganese in air for  $0.06$ ,  $0.3$ , and  $1.5 \text{ mg/m}^3$  for 7 and 13 weeks. Because  $1,500 \text{ } \mu\text{g/m}^3$  was the only dose administered at the lowest number of exposures (15 exposure days)—all other dose groups were exposed for more days— $1,500 \text{ } \mu\text{g/m}^3$  was selected as a lowest-observed-adverse-effect level (LOAEL). At  $1,500 \text{ } \mu\text{g/m}^3$ , manganese sulfate was reported to cause inflammatory airway changes (e.g., mild bronchitis, alveolar duct inflammation, see Attachment B). Applying an uncertainty factor of 300 to account for intraindividual variability (10-fold), interspecies variability (10-fold)<sup>9</sup>, and an adjustment from mild transient LOAEL to NOAEL (3-fold), results in a proposed TRV of  $5 \text{ } \mu\text{g/m}^3$ . This TRV is based on NHPs exposed to  $\text{MnSO}_4$ , which is freely soluble and considered the most bioavailable form of manganese. Therefore, in addition to being more

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<sup>9</sup> A lower 3-fold interspecies uncertainty factor could also be supported because a dosimetric adjustment between monkeys and humans is not required as discussed in Dorman et al. (2005). Using a 10-fold factor, the proposed TRV is conservative.

appropriate for 24-hour exposures than ODEQ's current TRV, the proposed TRV is more relevant to environmental exposures than the current TRV (which was developed based on workers exposed to less soluble manganese oxide).

### **3.2 Application of PBPK Model for Manganese to Assess Exposure at the Proposed TRV and SGC**

The PBPK model for manganese was developed to satisfy the United States Environmental Protection Agency (EPA) risk assessment requirements under the federal Clean Air Act. The model is able to predict the levels of manganese in the brain from exposure by diet and air for children (birth to 3 years) and youth to adults (3 years to adulthood) (Yoon et al. 2019). The current model code has been reviewed by the EPA's National Center for Environmental Assessment (NCEA).<sup>10</sup> EPA offered recommendations to improve the model, and those recommendations have been incorporated (Campbell et al., 2022; Attachment B). Importantly, the modifications to the model do not affect model predictions of manganese in the brain (Campbell et al., 2022).

Although neurological effects from acute exposures seem improbable, the previously published PBPK model for Mn exposure among infants, toddlers, children, and adults (Schroeter et al., 2011; Yoon et al., 2019) was applied to evaluate the potential for increased manganese concentration in the target tissue of the brain (i.e., globus pallidus) of humans exposed at the proposed TRV and SGC of 5 µg/m<sup>3</sup>. Specifically, two scenarios were modeled:

- 1) 24-hour exposures at the proposed TRV occurring once per month (monthly exposure scenario) throughout life, and
- 2) A continuous 3-week exposure occurring at the age when the model predicts the highest level of background manganese, which is approximately 3 years old (three week exposure scenario).

Use of the PBPK model reduces uncertainty regarding the potential for neurological effects in humans at the proposed TRV and SGC, which is based on, and specifically protective of, respiratory effects. It also allows for assessment of continuous (24-hour) exposure scenarios and of potentially sensitive exposure during early, sensitive life stages in humans. The PBPK model is based on exposures to MnSO<sub>4</sub>; therefore, no correction for bioavailability is needed.

The frequency of presumed 24-hour acute exposures is not specified in OAR 340-245-0020 (3). So, for this evaluation, the potential manganese accumulation in the brain from 24-hour exposure at the proposed TRV of 5 µg/m<sup>3</sup> was assumed to occur once per month (monthly exposure scenario) from birth to age 65. This frequency of acute exposures is considered conservative, because the TRV is compared to the highest 24-hour

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<sup>10</sup> Personal communication with Paul Schlosser, EPA NCEQ and Deborah Proctor, ToxStrategies.

concentration predicted using an air dispersion model and 5 years of meteorological data. Exposures to background levels of manganese in ambient air ( $0.015 \mu\text{g}/\text{m}^3$ ) (Gentry et al., 2017) were also assumed to occur for the rest of the time period.

The currently available model code, which is in R, does not allow for time-specific exposure periods. Thus, the model was expanded to allow for specifically timed exposures, in this case 24-hour exposures once per month, to predict uptake and distribution in the body. Importantly, this includes accumulation in the target tissue of the brain related to neurotoxic effects from manganese exposure (i.e., globus pallidus). In addition to accounting for age, the model is also specific to sex, so exposure to human females and human males, ages birth to 65 years, were modeled.

### 3.2.1 PBPK Modeling Methods

The current PBPK human model for Mn were developed from previous models in rats and monkeys (Schroeter et al. 2011; Yoon et al. 2019). These models characterized the toxicokinetics of Mn in the body following exposure by ingestion and inhalation and predict the target tissue concentrations in selected regions of the brain. The models also incorporate direct transport of Mn to the brain via the olfactory nerve (Schroeter et al., 2011). The animal models were extended to humans using tracer studies for verification. The Schroeter et al. (2011) and Yoon et al. (2019) model has simulated the results from  $^{54}\text{Mn}$  tracer kinetics from oral and inhalation exposures, and for multiple water-soluble manganese compounds. For inhalation, the model uses the Multiple-Path Particle Dosimetry Mode (MPPD model) to predict particle deposition in species-specific lung regions (Gentry et al., 2017).

We used the “lactation/infant” and the “child/adolescent/adult” model codes, as published most recently in Yoon et al. (2019), to estimate the manganese distribution in different sex and age groups. The full explanation of the human model is available in Schroeter et al. (2011) and Yoon et al. (2019) (Attachment D). The PBPK model accounts for dietary, drinking water, and inhalation exposure. The lactation/infant code simulates manganese kinetics in a lactating mother and a nursing child. It allows the simulation of manganese in a breast-fed and formula-fed infant for the first 6 months of life. Also, the code is applicable to simulate manganese distribution in children for the first three years of life. The child/adolescent/adult model code is applicable to simulate child, adolescent, and adult human exposure scenarios. The child and adolescent scenarios can simulate an age-dependent increase in tissue volumes, blood flows, and respiratory parameters from age 3 to 18. However, for the adult female and male scenarios simulation (>18 years), the model uses standard parameters for each sex at constant body weight.

### 3.2.2 Tissue-Based NOAELs in the Brain (Globus Pallidus)

Two studies (Schroeter et al., 2012; Gentry et al., 2017) have evaluated the dose-response for neurological effects associated with Mn exposure using the model-predicted Mn concentrations in the globus pallidus (i.e., target tissue for manganese toxicity in the brain) (Attachment C). In doing so, these authors incorporate the non-linear and dose-dependent kinetics of manganese in humans due to homeostasis. In the first (Schroeter et al., 2012),

the dose response was evaluated in NHPs for time frames of a few months to 2 years, using a categorical regression model (USEPA CatReg) software and severity scores for several neurological observations. For the inhalation studies, the dose was adjusted for particle deposition and solubility (Schroeter et al., 2012), and the Dorman et al. (2006) study, which used the same experimental design as Dorman et al. (2005), required no bioavailability adjustment, because manganese was administered as freely soluble  $\text{MnSO}_4$ .

Schroeter et al. (2012) reported a steep dose-response curve starting at peak manganese concentrations of 7  $\mu\text{g/g}$  globus pallidus for neurological effects. The CatReg-estimated Extra Risk Dose for 10% response (ERD10) for a severity score of 1 was a peak globus pallidus concentration of 0.8  $\mu\text{g/g}$ . For this reason, the ERD10 for a severity score of 1 (0.8  $\mu\text{g/g}$ ) is considered the tissue-based NOAEL using NHP data.

Gentry et al. (2017) conducted a similar study using the Schroeter et al. (2011) manganese PBPK model and measures of neurological effects among workers. Gentry et al. (2017) used blood Mn data as a biomarker and predicted the target tissue NOAEL from all available human studies, including Roels et al. (1992). In this study, Gentry et al. (2017) had access to the individual-level data on exposure and outcome from several studies, and blood Mn data from two studies, including Roels et al. (1992). A no-statistical-significance-of-trend (NOSTASOT) test was used with Fisher's exact test to predict target tissue Mn concentrations at the NOAELs for abnormal eye-hand coordination of 0.7  $\mu\text{g/g}$ , and 0.9  $\mu\text{g/g}$  for the endpoint of abnormal hand steadiness.

Schroeter et al. (2012) and Gentry et al. (2017) (Attachment C) provide highly consistent tissue NOAELs or thresholds for adverse effects, ranging from 0.7 to 0.9  $\mu\text{g/g}$ . Both studies also conclude that homeostatic control maintains tissue globus pallidus concentrations below these levels, for chronic inhalation exposures up to 10  $\mu\text{g/m}^3$ . It is also noteworthy as discussed below, that the tissue-based NOAELs for Mn in the globus pallidus are not substantially different than model predictions for background levels of Mn based on diet and background Mn in ambient air.

### 3.2.3 Acute Inhalation Exposure Modeling Results

We ran two scenarios using the PBPK model. For the monthly scenario, exposures were assumed to occur at the 5  $\mu\text{g/m}^3$  proposed TRV for 24 hours per day, for one day per month. Because the SGC is said to be for exposures of "a few weeks," we also modeled a 3-week scenario, in which exposures occurred at the 5  $\mu\text{g/m}^3$  for 24-hours per day, consecutively for three weeks. In both scenarios, all other exposures (oral and inhalation of ambient air) were set to background levels (dietary intake and background ambient air of 0.015  $\mu\text{g/m}^3$ ).

In the monthly scenario, the maximum manganese concentrations in the globus pallidus, whole blood, and liver remain relatively consistent with background levels (Table 2). The results are presented by demographics (age group and sex). The highest concentration in the globus pallidus (0.538  $\mu\text{g/g}$ ) of manganese is predicted for male children (3–10 years of age). The second-most susceptible demographic is female children (3 to 10 years of age), with a model-estimated manganese concentration of 0.517  $\mu\text{g/g}$ . These values are predicted



to occur around 3 years of age. The model predictions are only slightly above background and are well below the range of tissue-based NOAELs of 0.7 to 0.9 µg/g based on Schroeter et al. (2012) and Gentry et al. (2017). Thus, exposures to the proposed TRV for 24 hours per day, once per month, would not result in adverse neurotoxic effects.

**Table 2. Summary results of the monthly exposure scenario (24-hours per day, once-per-month exposure to 5 µg/m<sup>3</sup>)**

| Age Group                       | Manganese Concentration (µg/g) |             |                 |                 |
|---------------------------------|--------------------------------|-------------|-----------------|-----------------|
|                                 | Globus Pallidus                |             | Whole Blood     | Liver           |
|                                 | Model Predicted                | Back-ground | Model Predicted | Model Predicted |
| 0–0.5 years — Male neonate      | 0.368                          | 0.363       | 0.024           | 1.129           |
| 0.5–1 years — Male infant       | 0.327                          | 0.309       | 0.015           | 1.145           |
| 1–3 years — Male toddler        | 0.436                          | 0.431       | 0.018           | 1.202           |
| 3–10 years — Male child         | 0.538                          | 0.535       | 0.012           | 1.197           |
| 10–18 years — Male adolescent   | 0.476                          | 0.466       | 0.008           | 1.195           |
| >18 years — Male adult          | 0.391                          | 0.386       | 0.005           | 1.196           |
| 0–0.5 years — Female neonate    | 0.368                          | 0.363       | 0.024           | 1.130           |
| 0.5–1 years — Female infant     | 0.327                          | 0.309       | 0.015           | 1.145           |
| 1–3 years — Female toddler      | 0.436                          | 0.431       | 0.018           | 1.202           |
| 3–10 years — Female child       | 0.517                          | 0.514       | 0.013           | 1.199           |
| 10–18 years — Female adolescent | 0.436                          | 0.429       | 0.007           | 1.195           |
| >18 years — Female adult        | 0.347                          | 0.345       | 0.005           | 1.195           |

Because the TRV is based on the SGC, we also evaluated a 3-week exposure scenario. Because the monthly scenario predicts the highest manganese levels in the globus pallidus at approximately 3 years of age (Table 2), we modeled the 3-week scenario at age three for both females and males. In the 3-week scenario, the maximum globus pallidus concentration was 0.521 µg/g for females and 0.552 µg/g for males, which only slightly exceeds background (Table 3). Whole-blood and total liver concentrations were similar to the monthly scenario. Consistent with the results for the monthly scenario, levels of manganese in the globus pallidus for the 3-week scenario are well below the tissue-based NOAELs (0.7–0.9 µg/g). Thus, the model predicts that exposure for three weeks at the proposed SGC of 5 µg/m<sup>3</sup> would also not result in adverse neurotoxic effects.

These model predictions are consistent with Schroeter et al. (2012) and Gentry et al. (2017) which both predict that homeostasis maintains manganese levels in the target tissue of the brain at airborne exposures less than 10 µg/m<sup>3</sup> for long-term continuous exposures. The

current modeling work is presented in Perry et al. (2022) and in preparation for publication in the peer-reviewed scientific literature.

**Table 3. Summary table for the 3-week exposure scenario (daily inhalation exposure at 5 µg/m<sup>3</sup> for three weeks)**

| Age Group                 | Manganese Concentration (µg/g) |            |                 |                 |
|---------------------------|--------------------------------|------------|-----------------|-----------------|
|                           | Globus Pallidus                |            | Whole-Blood     | Liver           |
|                           | Model Predicted                | Background | Model Predicted | Model Predicted |
| 3–10 years — Female child | 0.521                          | 0.514      | 0.012           | 1.20            |
| 3–10 years — Male child   | 0.552                          | 0.535      | 0.012           | 1.20            |

## 4 Conclusion

The current TRV (and SGC) for acute manganese should be updated. The current TRV (and SGC) rely on chronic exposure levels provided by OEHHA, with an unsupported correction from chronic to subchronic exposures (reversing the subchronic-to-chronic extrapolation by OEHHA), and no provisions for subchronic to acute exposures. This is not consistent with relying on an “authoritative source.” OHA itself explicitly advised against using chronic values for acute exposure TRVs, particularly when (as here) the endpoints are not the same. No authoritative source specified in OAR 340-247-0030 has set TRVs, or their equivalent, for acute manganese exposures. In fact, both ATSDR and OEHHA explicitly declined to because there was insufficient scientific support to do so. Beyond being derived by an unsupported method, ODEQ’s current acute TRV for acute manganese exposure is excessively conservative, as evidenced by the fact that it is equal to ATSDR’s chronic MRL.

We petition ODEQ to change the acute manganese TRV to 5 µg/m<sup>3</sup>. The proposed value is consistent with the 24-hour AMCV developed by TCEQ, which was developed after a thorough literature review and addressing public comments. The proposed value is conservative, because it is based on mild, reversible respiratory effects observed after repeated exposures for a total of 60 hours over three weeks to Mn in air at 1,500 µg/m<sup>3</sup>, as reported by Dorman et al. (2005). To this LOAEL, a 300-fold uncertainty factor is appropriate, resulting in the proposed TRV of 5 µg/m<sup>3</sup>.

ATSDR (2012) identifies endpoints of potential concern associated with manganese exposure as neurotoxicity, reproductive and developmental toxicity, and respiratory toxicity. The proposed TRV based on Dorman et al. (2005) is protective of respiratory toxicity. Further, the reproductive and developmental toxicity study by McGough and Jardine (2017) involving subchronic exposures in rats at levels much higher than the proposed TRV (up to 8.1 mg/m<sup>3</sup> for up to 714 hours) did not result in reproductive or developmental toxicity, which reduces uncertainty associated with potential reproductive



or developmental effects. Additionally, Dorman et al. (2006) reported no observable symptoms of neurotoxicity associated with exposures in the 2005 study.

To further address any uncertainty as to whether neurotoxicity could pose a hazard to humans at the proposed TRV, we used the current human PBPK model to evaluate two exposure scenarios: reoccurring exposures for monthly 24-hour exposures (monthly scenario), and continuous exposure for 3 weeks at the age when manganese levels in brain are predicted to be highest (three week scenario). For both scenarios, the current human PBPK model was used to predict concentrations of manganese in blood, liver, and globus pallidus in males and females. The model predictions indicate that, at all life stages, the levels of manganese in the target tissue of the globus pallidus do not increase significantly over background levels and are lower than tissue NOAELs in the globus pallidus.

The proposed TRV of 5  $\mu\text{g}/\text{m}^3$  should be adopted by ODEQ, for these primary reasons:

- The current value is not based on authoritative sources.
- The proposed value is based on appropriate, peer-reviewed science that targets a relevant endpoint (respiratory system) for acute exposures.
- Other potential adverse effects related to manganese exposure (neurotoxic and reproductive/developmental) are not observed in peer-reviewed studies of exposures at this level.
- Applying the peer-reviewed PBPK model demonstrates that exposures at the proposed TRV would not result in accumulation in the brain that could result in neurotoxic effects.
- The proposed TRV has been established for 24-hour exposure by another state (Texas).

## 5. Supporting Information for Proposed Acute TRV for Mn

The following supporting documents are provided as attachments to this petition.

- Attachment A Dorman et al. (2005)
- Attachment B Summary of Relevant Toxicity Studies
- Attachment C Schroeter et al. (2012) and Gentry et al. (2017)
- Attachment D Schroeter et al. (2011), Yoon et al. (2019), Campbell et al. (2022)

## 6. References

ATSDR (Agency for Toxic Substances Disease Registry). 2012. Toxicological profile for Manganese. September.

Campbell J., Clewell, H, Gentry, R, et al. 2022. Incorporation of rapid association/dissociation processes in tissues into the monkey and human physiologically based pharmacokinetic models for manganese. Society of Toxicology Annual Meeting. San Diego, CA. Abstract 4035. Poster Board P734.

Dorman DC, et al. 2005. Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. *Respir Res* 6:121.

Dorman DC, et al. 2006. Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in Rhesus monkeys following subchronic manganese inhalation. *Toxicol. Sciences*. 92(1) 219-227.

Erikson KM. 2005. Persistent alterations in biomarkers of oxidative stress resulting from combined *in utero* and neonatal manganese inhalation. *Biol Trace Element Res* 14:151–163.

Gentry PR, et al. 2017. A tissue dose-based comparative exposure assessment of manganese using physiologically based pharmacokinetic modeling — The importance of homeostatic control for an essential metal. *Toxicol Appl Pharm* 322:27–40.

HaMai D, et al. 2006. Decreased expression of inflammation-related genes following inhalation exposure to manganese. *NeuroToxicology* 27:395–401.

McGough D, Jardine L. 2017. A two-generation inhalation reproductive toxicity study upon the exposure to manganese chloride. *NeuroToxicology* 58:194–202.

OEHHA (Office of Environmental Health Hazard Assessment). 2008a. Technical support document for the derivation of noncancer reference exposure levels. June 18.

OEHHA (Office of Environmental Health Hazard Assessment). 2008b. Technical support document for reference exposure levels (RELs). Appendix D. Individual acute, 8-hour, chronic reference exposure levels. Updated July 2014.

Perry, C., Vivanco, S., Antonijevic, T., Verwiel, A., Proctor, D. 2022. Short-Term Environmental Inhalation Toxicity Criteria for Airborne Manganese Protective of Neurological and Respiratory Effects for use in Air Toxics Risk Assessment (Platform Session). Society of Environmental Toxicology and Chemistry North America. 43<sup>rd</sup> annual meeting. Pittsburgh, PA. November.

Roels HA, et al. 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Brit J Ind Med* 49:25–34.

Sapputra D, et al. 2016. Short-term manganese inhalation decreases brain dopamine transporter levels without disrupting motor skills in rats. *J Toxicol Sci* 41(3):391–402.

Schroeter J, Nong A, Yoon M, et al. 2011. Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multi-route physiologically based pharmacokinetic models. *Toxicol Sci* 120(2):481–498.

Taylor et al., 2006. Effects of inhaled manganese on biomarkers of oxidative stress in the rat brain. *Neurotoxicology* 27:788–797.

TCEQ (Texas Commission on Environmental Quality). 2015. TCEQ guidelines to develop toxicity factors. Toxicology Division. Revised September 2015.

TCEQ (Texas Commission on Environmental Quality). 2017. Manganese and Inorganic Manganese Compounds, Development Support Document, Final. November 29.

U.S. EPA (U.S. Environmental Protection Agency). 2012. Benchmark dose technical guidance. EPA/100/R-12/001. June.

Yoon, et al. 2019. Assessing children's exposure to manganese in drinking water using a PBPK model. *Toxicol Appl Pharm* 380:114695.

## **ATTACHMENT A**

**Dorman et al. (2005)**

Research

Open Access

## Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys

David C Dorman\*<sup>1</sup>, Melanie F Struve<sup>1</sup>, Elizabeth A Gross<sup>1</sup>, Brian A Wong<sup>1</sup> and Paul C Howroyd<sup>2</sup>

Address: <sup>1</sup>CIIT Centers for Health Research, 6 Davis Drive, P.O. Box 12137, Research Triangle Park, NC 27709-2137, USA and <sup>2</sup>Experimental Pathology Laboratories, Inc., P.O. Box 12766, Research Triangle Park, NC 27709, USA

Email: David C Dorman\* - [dorman@ciit.org](mailto:dorman@ciit.org); Melanie F Struve - [struve@ciit.org](mailto:struve@ciit.org); Elizabeth A Gross - [gross@ciit.org](mailto:gross@ciit.org); Brian A Wong - [wong@ciit.org](mailto:wong@ciit.org); Paul C Howroyd - [paul.howroyd@bms.com](mailto:paul.howroyd@bms.com)

\* Corresponding author

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### Abstract

**Background:** Neurotoxicity and pulmonary dysfunction are well-recognized problems associated with prolonged human exposure to high concentrations of airborne manganese. Surprisingly, histological characterization of pulmonary responses induced by manganese remains incomplete. The primary objective of this study was to characterize histologic changes in the monkey respiratory tract following manganese inhalation.

**Methods:** Subchronic (6 hr/day, 5 days/week) inhalation exposure of young male rhesus monkeys to manganese sulfate was performed. One cohort of monkeys ( $n = 4-6$  animals/exposure concentration) was exposed to air or manganese sulfate at 0.06, 0.3, or 1.5 mg Mn/m<sup>3</sup> for 65 exposure days. Another eight monkeys were exposed to manganese sulfate at 1.5 mg Mn/m<sup>3</sup> for 65 exposure days and held for 45 or 90 days before evaluation. A second cohort ( $n = 4$  monkeys per time point) was exposed to manganese sulfate at 1.5 mg Mn/m<sup>3</sup> and evaluated after 15 or 33 exposure days. Evaluations included measurement of lung manganese concentrations and evaluation of respiratory histologic changes. Tissue manganese concentrations were compared for the exposure and control groups by tests for homogeneity of variance, analysis of variance, followed by Dunnett's multiple comparison. Histopathological findings were evaluated using a Pearson's Chi-Square test.

**Results:** Animals exposed to manganese sulfate at  $\geq 0.3$  mg Mn/m<sup>3</sup> for 65 days had increased lung manganese concentrations. Exposure to manganese sulfate at 1.5 mg Mn/m<sup>3</sup> for  $\geq 15$  exposure days resulted in increased lung manganese concentrations, mild subacute bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue. Bronchiolitis and alveolar duct inflammatory changes were absent 45 days post-exposure, suggesting that these lesions are reversible upon cessation of subchronic high-dose manganese exposure.

**Conclusion:** High-dose subchronic manganese sulfate inhalation is associated with increased lung manganese concentrations and small airway inflammatory changes in the absence of observable clinical signs. Subchronic exposure to manganese sulfate at exposure concentrations ( $\leq 0.3$  mg Mn/m<sup>3</sup>) similar to the current 8-hr occupational threshold limit value established for inhaled manganese was not associated with pulmonary pathology.

## Background

There is growing evidence to suggest that a wide variety of respirable particles can induce lung injury under certain exposure conditions. Clinical recognition of this hazard originally stemmed from occupational studies examining workplace exposure to metals, asbestos, silica, coal, and other biologically active particles [1,2]. However, particulate-induced lung injury is not confined to the workplace. There is strong epidemiologic evidence for significant associations between respiratory morbidity, including exacerbations of asthma and mortality, with exposure to relatively low ambient particulate matter concentrations [3,4]. This association has contributed to the adoption of more stringent ambient air quality standards for respirable particulate matter by the United States Environmental Protection Agency and other health organizations.

Particulate matter is not a single entity but rather a mixture of many subclasses of pollutants including metals, sulfate, acids, ammonium, nitrate, organic compounds, and minerals. Depending on emission source, metals may represent a significant proportion of a particulate matter sample [5]. Soluble metals have been implicated in particulate matter-associated cardiopulmonary disease in healthy and compromised individuals [6-8]. One metal found in ambient air is manganese. Airborne manganese sources include wind erosion of dusts and soils, anthropogenic fugitive dusts, and emissions from automobiles, power plants, coke ovens, municipal waste incinerators, and metal smelting operations [5]. Ambient air manganese concentrations are typically quite low, ranging between 5 and 33 ng Mn/m<sup>3</sup> [9]. Significant occupational manganese exposure ( $\geq 0.2$  mg Mn/m<sup>3</sup>) can occur in some workers involved in ferroalloy production, iron and steel foundries, and welding [9].

Workers exposed to high atmospheric manganese concentrations frequently demonstrate an increased incidence of cough and other signs associated with bronchitis [10,11]. Acute inhalation of air with extremely high manganese concentrations ( $\geq 1$  mg Mn/m<sup>3</sup>) can result in pneumonitis [12]. Although manganese-induced pneumonitis has been recognized since the mid-1940's, histological characterization of the pulmonary response remains incomplete. Most experimental exposures in laboratory animals have shown only minor lung pathology despite the administration of high doses of manganese oxides by intratracheal instillation or inhalation [13-18]. Far less is known about the potential respiratory effects induced by exposure to other inorganic forms of manganese. Manganese chloride instillation into rabbits failed to induce significant pulmonary pathology [19]. Dorman et al. [20] showed that subchronic exposure of rats to manganese sulfate (MnSO<sub>4</sub>) was associated with rhinitis in the anterior part of the nose. To our knowledge, histologic assess-

ment of pulmonary changes occurring in association with subchronic inhalation of MnSO<sub>4</sub> has not been performed and is the subject of our study. Herein, we report that subchronic high-dose inhalation exposure of nonhuman primates to MnSO<sub>4</sub> resulted in mild subacute bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue (BALT), in the absence of rhinitis or other forms of nasal pathology.

## Methods

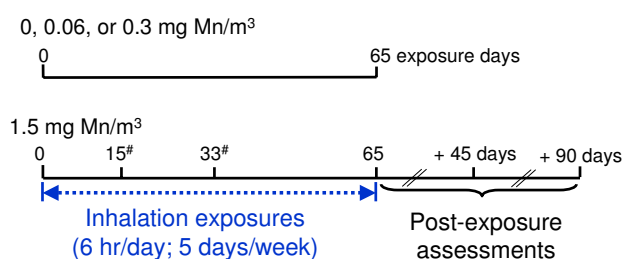
### Chemicals

Manganese (II) sulfate monohydrate (MnSO<sub>4</sub> · H<sub>2</sub>O) was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI).

### Animals

This study was conducted under federal guidelines for the care and use of laboratory animals [21] and was approved by the CIIT Centers for Health Research (CIIT) Institutional Animal Care and Use Committee. Additional endpoints evaluated in this study, but not presented in the present manuscript, included determination of manganese concentrations in additional tissues and magnetic resonance imaging (MRI) of the brain. We chose to use rhesus monkeys since they are extensively used in toxicology studies, manganese-exposed monkeys develop distribution patterns for this metal within the brain that mimic those seen in heavily exposed people [22], and there are anatomically-based simulation models for air flow in the macaque upper and lower respiratory tracts [23,24]. Thirty-six male rhesus monkeys purchased from Covance Research Products, Inc. (Alice, TX) were used in this study. Monkeys were 17 to 22 months old at the time of their arrival at CIIT. Animals were screened for the nasal parasite *Anatrichosoma* spp. herpes B, simian immunodeficiency virus, simian respiratory virus, pulmonary acariasis, and tuberculosis, and were subjected to a thorough clinical examination including an evaluation of pre-exposure blood samples for routine hematology and clinical chemistry. The results of these evaluations were within normal limits.

Assignment of animals to treatment cohorts considered the age of the animal. Assignment occurred so that the animals were between 20 and 24 months of age at the start of the inhalation exposure. Randomization of animals to treatment groups occurred prior to the start of the inhalation exposure and was based upon a weight randomization procedure. Animals were acclimated to the facility for at least 43 days prior to the start of the first inhalation exposure. Additional endpoints evaluated in this study, but not presented in the present manuscript, included magnetic resonance imaging (MRI) of the brain, post-exposure clinical chemistry and hematological evaluations, and determination of tissue manganese

**Figure 1**

**Experimental design overview.** Group size equals 4 monkeys per exposure group, with the exception of the 0 and 0.06 mg Mn/m<sup>3</sup> exposure groups (n = 6 monkeys/exposure concentration). Lung manganese concentrations and respiratory histologic changes were evaluated after 15, 33, or 65 exposure days or 45 or 90 days after the 65<sup>th</sup> exposure day. #Denotes animals assigned to cohort 2.

concentrations in the central nervous system and other organs.

#### Animal Husbandry

Animal rooms were maintained at daily temperatures of 22 ± 4°C, relative humidity of 30–70%, and an air flow rate sufficient to provide 10–15 air changes per hour. Lighting was controlled by automatic controls (lights on approximately 0600–1800). All exposures were conducted during the animal's light cycle (approximately from 0800 to 1400). All animals were housed in animal rooms or exposure chambers within CIIT's animal facility. This facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. A certified primate chow (# 5048) diet from Purina Mills (St. Louis, MO) was fed twice-a-day (total daily amount fed was approximately 4% of the animal's body weight). Dietary supplements were also used as part of CIIT's nonhuman primate enrichment program. These supplements included fruits (e.g., oranges, raisins, apples), vegetables (e.g., carrots), and treats (e.g., honey, candies, cereal, fruit juices) purchased from a local grocery store. Reverse osmosis purified water was available *ad libitum*. During non-exposure periods, domiciliary stainless steel cages (0.4 m<sup>2</sup> × 0.8 m tall) suitable for housing macaque monkeys (Lab Products, Inc.; Seaford, DE) were used to individually house monkeys. On each exposure day, animals were transferred to 0.2 m<sup>2</sup> × 0.6 m tall stainless steel cages (Lab Products, Inc.; Seaford, DE) that were designed to fit within the 8-m<sup>3</sup> inhalation chambers. Animals were moved back to their domiciliary cages after the end of each 6-hr exposure.

#### Manganese Exposures

MnSO<sub>4</sub> aerosol concentrations of 0.18, 0.92, and 4.62 mg MnSO<sub>4</sub>/m<sup>3</sup>, corresponding to 0.06, 0.3, and 1.5 mg Mn/m<sup>3</sup>, were generated for this study. Control animals were exposed to filtered air. Animal exposures were conducted as described in Figure 1. Four 8-m<sup>3</sup> stainless steel and glass inhalation exposure chambers with glass doors and windows for animal observation were used. Animal position within the inhalation chambers was rotated weekly to minimize the impact of any undetected differences in the environment or in the MnSO<sub>4</sub> exposure concentrations. Air flow through the 8-m<sup>3</sup> inhalation chamber was typically maintained at a rate sufficient to provide at least 12 air changes per hour. Airflow through each chamber was monitored continuously during each exposure and recorded every 30 minutes. Temperature and relative humidity inside each inhalation chamber were recorded every 30 minutes during each 6-hr exposure. The average chamber temperature and relative humidity during the 6-hr exposure period were maintained at 18–26°C and 50 ± 20%, respectively. Methods describing the generation of the MnSO<sub>4</sub> atmosphere with a dry powder generator (Wright Dust Feeder, Model WDF-II, BGI, Inc., Waltham, MA) and the characterization of the subsequent aerosol have been previously described [25]. MnSO<sub>4</sub> was packed in separate dry powder generator cups at pressures between 2000 and 3000 psi (Model 3912, Carver Inc., Wabash, IN) using a hydraulic press (Model C, Carver Inc., Menomonee Falls, WI).

#### Necropsy Procedures

Necropsies were performed the day following the last inhalation exposure (i.e., 12–18 hr after termination of the final inhalation exposure). Food was withheld overnight prior to necropsy. Monkeys were anesthetized with ketamine (20 mg/kg, IM, Fort Dodge Animal Health, Fort Dodge, IA) and euthanized with pentobarbital (80–150 mg/kg, IV, Henry Schein Inc., Port Washington, NY) followed by exsanguination. Following euthanasia, the lungs and other thoracic organs were removed, weighed, and inspected for gross lesions. The left primary bronchus was ligated and the left lung separated for determination of tissue manganese concentration. The right lung and trachea were then inflated with 10% neutral-buffered formalin using 30-cm of hydrostatic pressure [26]. The olfactory epithelium was excised for chemical analysis and the remaining nasal tissues, including the nasopharynx and larynx, were stored in 10% neutral-buffered formalin. The larynx samples were decalcified in 10% formic acid (Fisher Scientific International, Inc., Hampton, NH) for two days. Cranial tissues were decalcified in RDO® (Apex Engineering Products Corporation, Plainfield, IL) for up to 6 days. Following decalcification, tissues were washed in running tap water for at least 6 hr. Following fixation (and decalcification when appropriate), representative

**Table 1: Characteristics of manganese aerosols generated for whole-body exposures in this study (means  $\pm$  SD)**

|                                                                                    | Nominal MnSO <sub>4</sub> exposure concentration (mg/m <sup>3</sup> ) |                 |                   |                   |
|------------------------------------------------------------------------------------|-----------------------------------------------------------------------|-----------------|-------------------|-------------------|
|                                                                                    | 0.18                                                                  | 0.92            | 4.62 <sup>a</sup> | 4.62 <sup>b</sup> |
| Actual exposure concentration (mg MnSO <sub>4</sub> /m <sup>3</sup> ) <sup>c</sup> | 0.19 $\pm$ 0.01                                                       | 0.97 $\pm$ 0.06 | 4.55 $\pm$ 0.33   | 4.45 $\pm$ 0.35   |
| Geometric mean diameter ( $\mu$ m) <sup>d</sup>                                    | 1.04                                                                  | 1.07            | 1.12              | 1.04              |
| Geometric standard deviation ( $\sigma_g$ ) <sup>d</sup>                           | 1.51                                                                  | 1.54            | 1.58              | 1.50              |
| Mass median aerodynamic diameter ( $\mu$ m) <sup>e</sup>                           | 1.73                                                                  | 1.89            | 2.12              | 1.72              |

<sup>a</sup> Cohort 1<sup>b</sup> Cohort 2<sup>c</sup> Based on continuous chamber monitoring with a calibrated optical particle sensor (Real-Time Aerosol Sensors, Model RAM-S, MIE, Inc., Billerica, MA).<sup>d</sup> Based on biweekly aerodynamic particle size spectrometry (Aerodynamic Particle Sizer, Model 3320, TSI, Inc., St. Paul, MN) measurements.<sup>e</sup> Calculated value [56]

samples of the lung, trachea, larynx, oropharynx, tracheo-bronchial lymph nodes, and nose were collected from each animal. Tissue samples were trimmed, embedded in paraffin, and five- $\mu$ m thick sections were cut and stained with hematoxylin and eosin for light microscopic evaluation. Histologic specimens were examined by an experienced veterinary pathologist (Howroyd).

#### Tissue manganese concentrations

Tissue samples collected for chemical analyses were stored in individual plastic containers, frozen in liquid nitrogen, and stored at approximately -80°C until chemical analyses were performed. Lung and olfactory epithelium manganese concentrations were determined by graphite furnace atomic absorption spectrometry using previously published methods [27].

#### Statistics

Tissue manganese concentrations were compared for the exposure and control groups by tests for homogeneity of variance (Levene's test), analysis of variance (ANOVA), and Dunnett's multiple comparison procedure for significant ANOVA. Histopathological findings were evaluated using a Chi-Square test. Statistical analyses were performed using SAS Statistical Software. A probability value of <0.01 was used for Levene's test, while <0.05 was used as the critical level of significance for all other statistical tests. Unless otherwise noted, data presented are mean values  $\pm$  standard error of the mean (SEM).

## Results

#### Test atmospheres

No significant differences in the test aerosol characteristics were observed between the two exposure cohorts (Table 1). Particles of unknown composition (arising from animal dander and other background sources) were present in the control chamber at an overall average concentration  $\pm$  standard deviation (SD) of 0.004  $\pm$  0.002 mg/m<sup>3</sup>. The

calculated mass median aerodynamic diameter (MMAD) for the particles in the control chamber was 3.9  $\mu$ m.

#### Lung and olfactory epithelium manganese concentrations following MnSO<sub>4</sub> exposure

Lung and olfactory epithelium manganese concentrations are presented in Table 2. Animals exposed to MnSO<sub>4</sub> at  $\geq$ 0.3 mg Mn/m<sup>3</sup> for 65 exposure days developed increased lung manganese concentrations. Animals exposed to MnSO<sub>4</sub> at  $\geq$ 0.06 mg Mn/m<sup>3</sup> for 65 exposure days developed increased olfactory epithelium manganese concentrations. Increased lung and olfactory epithelium manganese concentrations developed within three weeks of exposure to MnSO<sub>4</sub> at 1.5 mg Mn/m<sup>3</sup>. Within 45 days after completion of the 65-day inhalation exposure to MnSO<sub>4</sub> at 1.5 mg Mn/m<sup>3</sup> regimen, lung and olfactory epithelium manganese concentrations were not different from those seen in air-exposed controls.

#### Respiratory tract pathology following MnSO<sub>4</sub> exposure

Manganese exposure did not affect absolute or relative lung weights and did not result in coughing, dyspnea, or other respiratory signs (data not shown). High-dose exposure to MnSO<sub>4</sub> was associated with an increased incidence of minimal to mild subacute bronchiolitis (Table 3). These lesions consisted of infiltrates of lymphocytes, along with neutrophils and occasional eosinophils, primarily surrounding the terminal and respiratory bronchioles and/or alveolar ducts, but sometimes extending into the lamina propria (Figure 2). Macrophages with moderate amounts of pale-staining cytoplasm were occasionally observed in the adjacent airway lumen. Although the overlying epithelium generally appeared intact, because it is normally very thin at the level of the distal airways, it is difficult to confirm that epithelial integrity was unaffected. These changes appeared to be reversible upon cessation of MnSO<sub>4</sub> exposure. An increased incidence of enhanced proliferation of BALT in association with



**Table 2: Olfactory epithelial and lung manganese concentrations in young monkeys following exposure to air or MnSO<sub>4</sub>. Manganese concentrations were determined by graphite furnace atomic absorption spectrometry and are expressed as mean ± SEM µg Mn/g tissue wet weight. Young male rhesus monkeys (n = 4 except where noted) were exposed to either air or MnSO<sub>4</sub> 6 hours/day, 5 days/week.**

| Tissue               | MnSO <sub>4</sub> exposure concentration (mg Mn/m <sup>3</sup> ) | 15                       | 33                       | Exposure Day 65           | 65 [+45] <sup>a</sup> | 65 [+90] <sup>a</sup> |
|----------------------|------------------------------------------------------------------|--------------------------|--------------------------|---------------------------|-----------------------|-----------------------|
| Olfactory epithelium | 0                                                                |                          |                          | 0.42 ± 0.01 <sup>b</sup>  |                       |                       |
|                      | 0.06                                                             |                          |                          | 1.22 ± 0.15 <sup>*b</sup> |                       |                       |
|                      | 0.3                                                              |                          |                          | 2.96 ± 0.46 <sup>*</sup>  |                       |                       |
|                      | 1.5                                                              | 6.10 ± 0.39 <sup>*</sup> | 7.34 ± 0.70 <sup>*</sup> | 7.10 ± 2.01 <sup>*</sup>  | 0.65 ± 0.04           | 0.69 ± 0.11           |
| Lung                 | 0                                                                |                          |                          | 0.15 ± 0.03 <sup>b</sup>  |                       |                       |
|                      | 0.06                                                             |                          |                          | 0.18 ± 0.01 <sup>b</sup>  |                       |                       |
|                      | 0.3                                                              |                          |                          | 0.25 ± 0.02 <sup>*</sup>  |                       |                       |
|                      | 1.5                                                              | 0.39 ± 0.06 <sup>*</sup> | 0.35 ± 0.02 <sup>*</sup> | 0.33 ± 0.04 <sup>*</sup>  | 0.09 ± 0.01           | 0.06 ± 0.01           |

<sup>a</sup> Number in brackets indicates number of days post exposure assessment.

<sup>b</sup> n = 6.

<sup>\*</sup> p < 0.05

**Table 3: Incidence of MnSO<sub>4</sub>-induced microscopic lesions observed in young male rhesus monkeys exposed to MnSO<sub>4</sub>. Incidence is expressed as number affected/number examined.**

| Lesion                                            | MnSO <sub>4</sub> exposure concentration (mg Mn/m <sup>3</sup> ) | 15               | 33               | Exposure Day 65  | 65 [+45] <sup>a</sup> | 65 [+90] <sup>a</sup> |
|---------------------------------------------------|------------------------------------------------------------------|------------------|------------------|------------------|-----------------------|-----------------------|
| Subacute bronchiolitis/alveolar duct inflammation | 0                                                                |                  |                  | 0/6              |                       |                       |
|                                                   | 0.06                                                             |                  |                  | 0/6              |                       |                       |
|                                                   | 0.3                                                              |                  |                  | 1/4 <sup>b</sup> |                       |                       |
|                                                   | 1.5                                                              | 3/4 <sup>*</sup> | 4/4 <sup>*</sup> | 3/4 <sup>*</sup> | 0/4                   | 1/4                   |
| Increased bronchus associated lymphoid tissue     | 0                                                                |                  |                  | 0/6              |                       |                       |
|                                                   | 0.06                                                             |                  |                  | 0/6              |                       |                       |
|                                                   | 0.3                                                              |                  |                  | 1/4              |                       |                       |
|                                                   | 1.5                                                              | 2/4 <sup>†</sup> | 3/4 <sup>*</sup> | 1/4              | 2/4 <sup>†</sup>      | 1/4                   |

<sup>a</sup> Number in brackets indicates number of days post exposure assessment

<sup>b</sup> Subacute bronchiolitis was observed in one monkey; however, in this animal only, this lesion was observed in conjunction with aspirated food particles.

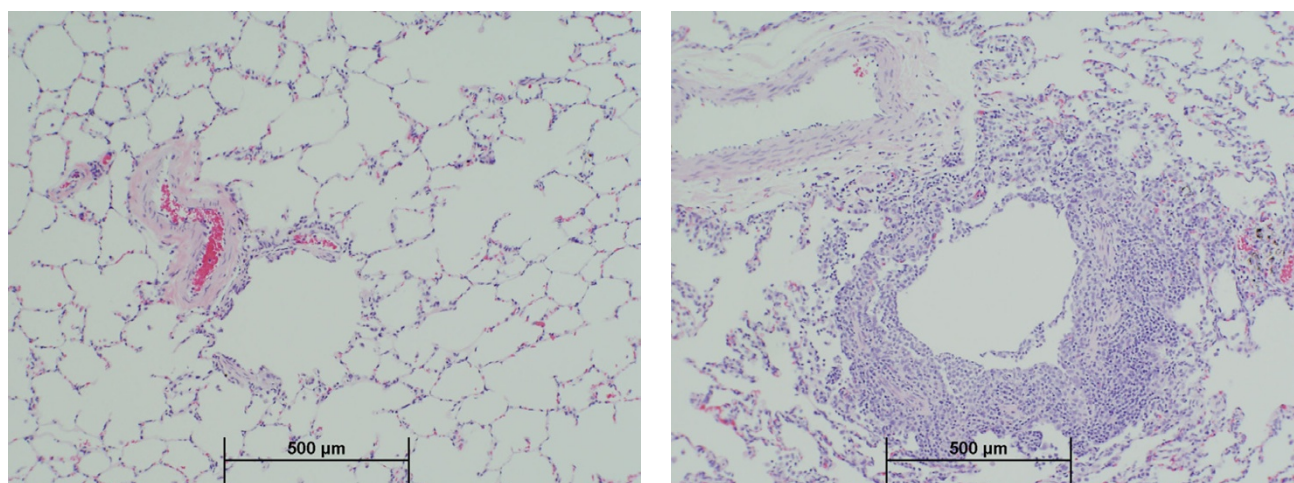
<sup>\*</sup> p < 0.05 (Pearson's chi-square test)

<sup>†</sup> p = 0.053 (Pearson's chi-square test)

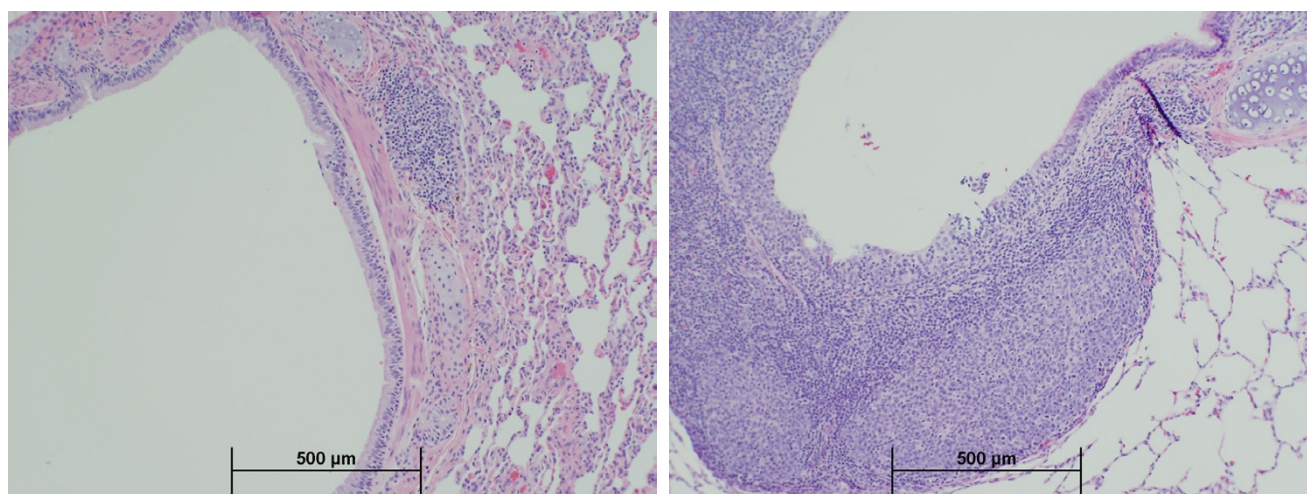
smaller (≤500 µm) airways also occurred in monkeys exposed to the highest MnSO<sub>4</sub> concentration (1.5 mg Mn/m<sup>3</sup>) (Figure 3). Some BALF foci included germinal center formation. The incidence of increased BALF was highest in monkeys exposed to 1.5 mg Mn/m<sup>3</sup> for 33 exposure days (Table 3) suggesting that BALF proliferation may subside even in the face of ongoing manganese exposure. Proliferation of BALF occurred in one animal exposed to

MnSO<sub>4</sub> at 0.3 mg Mn/m<sup>3</sup>; however, this increase was only minimal and was not statistically significant.

Several of the MnSO<sub>4</sub>-exposed animals had minimal acute alveolitis. However, this finding was considered unlikely to be treatment-related since no statistically significant dose-response relationship was observed. Minimal changes consistent with chronic bronchiolitis were

**Figure 2**

**Bronchiolitis.** Moderate subacute bronchiolitis in a monkey exposed to the highest ( $1.5 \text{ mg Mn/m}^3$ )  $\text{MnSO}_4$  exposure concentration for 15 exposure days (right). Normal appearing bronchioles present in an air-exposed control monkey (left). ( $10\times$ )

**Figure 3**

**BALT proliferation.** Peribronchial BALT proliferation in a monkey exposed to the highest ( $1.5 \text{ mg Mn/m}^3$ )  $\text{MnSO}_4$  exposure concentration for 65 exposure days (right). Normal appearing BALT present in an air-exposed control monkey (left). ( $4\times$ )

observed in several control as well as  $\text{MnSO}_4$ -exposed animals. As such, these changes were not considered to be treatment-related. The majority of lung sections examined, including those taken from controls, had scattered deposits of brown-green pigment in the interstitial tissue. Such chronic bronchiolitic changes characterized by lung pigment deposits are commonly seen in monkeys

with lung mites [28,29]. The most common lung mite is *Pneumonyssus simicola* and this agent occurs with nearly 100% incidence in rhesus monkeys [28,29]. Animals used on this study were treated with ivermectin prior to use; thus it is unlikely that superimposed active mite infection occurred. This conclusion is further supported by the absence of microscopic evidence of mites.

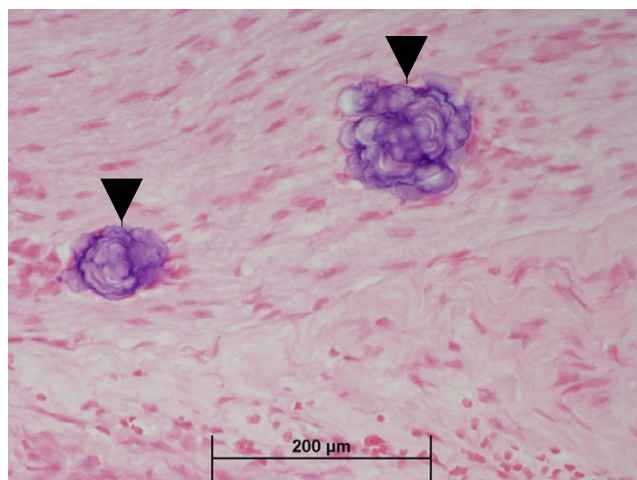


**Figure 4**  
**Basophilic foci in nerves.** Basophilic foci (arrow) in nerves of olfactory mucosa from a monkey exposed to  $\text{MnSO}_4$  at  $0.06 \text{ mg Mn/m}^3$ , for 65 days ( $40\times$ ).

One animal from each of the  $0.06$  and  $1.5 \text{ mg Mn/m}^3$  exposure groups had minimal or mild, basophilic foci in the nerves of the nose. The spherical basophilic foci were approximately  $40 \mu\text{m}$  in diameter and consisted of concentric lamellae (Figure 4). The foci were Periodic acid-Schiff stain positive but failed to stain with alizarin red, von Kossa's, or Perl's stains (for calcium or iron) and were not birefringent in polarized light (data not shown). Similar foci were present in the nasal epithelium of three other animals, including one control animal. Thus, it is unlikely that these foci were induced by  $\text{MnSO}_4$  exposure. X-ray microanalysis of foci taken from the decalcified nasal epithelium of a single monkey from the  $1.5 \text{ mg Mn/m}^3$  exposure group showed the presence of sulfur but no other ions (data not shown). Thus, the basophilic foci noted in the nasal nerves were most likely glycoproteinaeous inclusion bodies (i.e., corpora amylacea) or psammoma bodies. Similar deposits have been observed in the olfactory nerves of untreated rhesus monkeys and rats (Howroyd, unpublished observations), in the olfactory tracts of humans [30], and in the brains of mice [31] and monkeys [32,33].

## Discussion

Pulmonary inflammation is a common response to the inhalation of various types of particles including manganese [34]. In the present study, monkeys exposed to the highest  $\text{MnSO}_4$  concentration ( $1.5 \text{ mg Mn/m}^3$ ) developed subacute bronchiolitis and proliferation of BALT. Bronchiolitis included an infiltrate of acute inflammatory cells

(neutrophils) in the peribronchiolar connective tissues in the centriacinar region. These lesions developed relatively rapidly as they were observed in monkeys exposed to  $\text{MnSO}_4$  for only 15 exposure days. However, with ongoing  $\text{MnSO}_4$  exposure, the bronchiolitic lesion progressed, affecting a larger percentage of respiratory bronchioles examined. Bronchiolitis resolved rapidly after cessation of  $\text{MnSO}_4$  exposure and was absent 45 days after the end of the 13 week exposure to  $\text{MnSO}_4$  at  $1.5 \text{ mg Mn/m}^3$ .

Monkeys and human beings share similar lung anatomy [35], and their respiratory bronchioles and other small airways have similar sensitivity to inhaled toxicants such as cigarette smoke, coal dust, and ozone [36-38].

Following bronchiolitis, people are often noted to have increased wheeze, cough, and asthma, increased airway responsiveness, and reduced lung function due primarily to airflow obstruction [39]. In the present study, signs referable to the respiratory system were not recognized in the monkeys developing manganese-induced bronchiolitis. Although pulmonary function was not assessed in our study, reduced forced expiratory volume in one second ( $\text{FEV}_{10}$ ) and forced vital capacity (FVC) have been reported in workers that have been chronically exposed to high levels of manganese dust [10,40].

Particles deposited in the lung can be retained in the lung interstitium [41] or cleared via the mucociliary apparatus or through the lymphatic system [42]. Alternatively, particles may be transported from the lung via alveolar macrophages or neutrophils with subsequent accumulation in the BALT and tracheobronchial lymph node [42,43]. Thus, as a lymphoepithelial organ, the BALT is critical to the immune defense of the lung and to alveolar clearance of particles and lung pathogens. Proliferation of BALT has been observed in rodents following inhalation exposure to carbon black and silica [44,45]. There is evidence that BALT proliferation occurs in humans with panbronchiolitis, chronic hypersensitivity pneumonitis, and other chronic inflammatory airway disease [46,47]. Proliferative BALT lesions observed in these disease conditions are comparable to those observed in the  $\text{MnSO}_4$ -exposed monkeys, suggesting that BALT proliferation in the manganese-exposed monkeys may be related to the local airway immune response secondary to inflammation induced by  $\text{MnSO}_4$ .

Some agents that target the lung may also affect the upper airways as well. Our laboratory has recently reported that rats exposed subchronically to  $\text{MnSO}_4$  (at  $0.5 \text{ mg Mn/m}^3$ ) develop a mild reversible inflammatory change consisting of pleocellular inflammatory infiltrates and fibrinonecrotic debris within the nasal respiratory epithelium [20]. These lesions occurred primarily in high airflow

regions and were consistent with mild irritation. In the present study, however, despite a 15-fold increase in nasal epithelial manganese concentrations, we did not observe any chemical-related nasal pathology in monkeys exposed to  $\text{MnSO}_4$ . Although nasal pathology did not occur, the fate of the manganese that is initially deposited in the nose and subsequently absorbed by the olfactory epithelium remains toxicologically important. Experiments from our laboratory have shown that manganese deposited on the olfactory epithelium can undergo transport along the olfactory nerve with subsequent delivery to the olfactory bulb [48].

Our interest in  $\text{MnSO}_4$  stems from the use of manganese in the gasoline fuel additive methylcyclopentadienyl manganese tricarbonyl (MMT). Automobiles that use MMT in the fuel and are equipped with catalytic converters emit manganese primarily in the phosphate and sulfate forms with smaller amounts of manganese oxides also being discharged [49]. The manganese exposure concentrations used in this study bracket several human exposure scenarios. Prolonged human exposure to the highest  $\text{MnSO}_4$  concentration used in this study ( $1.5 \text{ mg Mn/m}^3$ ) can occur among manganese miners and prolonged exposure is associated with frank neurotoxicity and respiratory disease [9]. Our mid-dose exposure concentration is analogous to the current 8-hr Threshold Limit Value (TLV) for inhaled manganese of  $0.2 \text{ mg Mn/m}^3$  that has been established by the American Conference of Governmental Industrial Hygienists (ACGIH). Our lowest exposure concentration ( $0.06 \text{ mg Mn/m}^3$ ) is  $> 2,000$ -fold higher than typical air manganese concentrations observed in the ambient air including Canadian cities where MMT is extensively used in gasoline [9,50]. In the present study, exposure concentrations associated with increased lung manganese concentrations and lung pathology were respectively 1.5- and 7.5-fold higher than the current TLV.

The  $\text{MnSO}_4$  particle size used in this study had an MMAD of 1.72 to  $2.12 \mu\text{m}$ . Aerodynamic size is an important factor that influences particle deposition [51]. Several models based on airway geometry have been developed to describe particle deposition patterns in humans, monkeys, and rats [52,53]. The model of Asgharian and coworkers (1995) predicts a pulmonary deposition efficiency of an aerosol with a particle size of  $1.5 \mu\text{m}$  of approximately 35% for humans and rhesus monkeys while the rat had much lower deposition efficiency (6%) due to higher nasal uptake [52]. The rate of particle clearance from the alveolar region also differs among species. Rodents clear particles from the lung more quickly than either monkeys or humans [54]. Anatomical differences between rodents and primates also affect particle deposition, retention, and clearance. Rodents lack respiratory bronchioles and have simple acini. Macaque monkeys

and humans have larger alveoli and alveolar ducts than rats [55] and have similar numbers of respiratory bronchiole generations between the terminal bronchiole and the alveolar duct [35,56]. Our results may be especially important for human risk assessment owing to the fact that monkeys and human beings share similar lung anatomy (i.e., both species have extensive respiratory bronchioles comprised of bronchiolar epithelium and gas exchange epithelium) [35].

## Conclusion

High-dose subchronic manganese sulfate inhalation is associated with increased lung manganese concentrations, mild subacute bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue. Bronchiolitis and alveolar duct inflammatory changes were absent 45 days post-exposure, suggesting that these lesions are reversible upon cessation of subchronic high-dose manganese exposure. These small airway changes occurred in the absence of observable clinical signs. Subchronic exposure to manganese sulfate at exposure concentrations ( $\leq 0.3 \text{ mg Mn/m}^3$ ) similar to the current 8-hr occupational threshold limit value established for inhaled manganese was not associated with pulmonary or nasal pathology.

## Competing interests

This publication is based on a study sponsored and funded by Afton Chemical Corporation in satisfaction of registration requirements arising under Section 211(a) and (b) of the Clean Air Act and corresponding regulations at 40 C. F. R. Subsections 79.50 *et seq.*

## Authors' contributions

DCD conceived of the study, was the principal investigator and participated in all phases of the study, and drafted the manuscript. MFS participated in the design, coordination, and conduct of the study. EAG participated in and supervised the necropsy and preparation of histology specimens. BAW designed the exposure generation system and characterization of the aerosol. PCH was the study pathologist and conducted the histopathological evaluation of tissues. All authors contributed to, read, and approved the final manuscript.

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## References

1. De Vuyst P, Camus P: **The past and present of pneumoconioses.** *Curr Opin Pulm Med* 2000, **6**:151-156.
2. Kelleher P, Pacheco K, Newman LS: **Inorganic dust pneumonias: the metal-related parenchymal disorders.** *Environ Health Perspect* 2000, **108**(Suppl 4):685-696.



3. Pope CA 3rd: **What do epidemiologic findings tell us about health effects of environmental aerosols?** *J Aerosol Med* 2000, **13**:335-354.
4. Schwartz J: **Air pollution and daily mortality: a review and meta analysis.** *Environ Res* 1994, **64**:36-52.
5. United States Environmental Protection Agency (U.S. EPA): *Air Quality Criteria for Particulate Matter. EPA/600/P-95/001 Volume 2.* Washington DC: Office of Research and Development; 1996.
6. Chapman RS, Watkinson WP, Dreher KL, Costa DL: **Ambient particulate matter and respiratory and cardiovascular illness in adults: particle-borne transition metals and the heart-lung axis.** *Environ Toxicol Pharmacol* 1997, **4**:331-338.
7. Costa DL, Dreher KL: **Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models.** *Environ Health Perspect* 1997, **105**(Suppl 5):1053-1060.
8. Gavett SH, Madison SL, Dreher KL, Winsett DW, McGee JK, Costa DL: **Metal and sulfate composition of residual oil fly ash determines airway hyperreactivity and lung injury in rats.** *Environ Res* 1997, **72**:162-172.
9. Agency for Toxic Substances and Disease Registry (ATSDR): *Toxicological Profile for Manganese* Atlanta, GA: US Department of Health and Human Services; 2000.
10. Roels H, Lauwerys R, Buchet JP, Genet P, Sarhan MJ, Hanotiau I, deFays M, Bernard A, Stanesco D: **Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices.** *Am J Ind Med* 1987, **11**:307-327.
11. Saric M: **Occupational and environmental exposures and non-specific lung disease – a review of selected studies.** *Isr J Med Sci* 1992, **28**:509-512.
12. Lloyd Davies TA, Harding HE: **Manganese pneumonitis. Further clinical and experimental observations.** *Br J Ind Med* 1949, **6**:82-90.
13. Adkins B Jr, Luginbuhl GH, Gardner DE: **Acute exposure of laboratory mice to manganese oxide.** *Am Ind Hyg Assoc J* 1980, **41**:494-500.
14. Bergstrom R: **Acute pulmonary toxicity of manganese dioxide.** *Scand J Work Environ Health* 1977, **3**(Suppl 1):1-41.
15. Shanker R, Dogra RK, Sahu AP, Zaidi SH: **Experimental manganese lymphadenopathy in guinea pigs.** *Arch Toxicol* 1976, **36**:151-157.
16. Singh J, Kaw JL, Zaidi SH: **Early biochemical response of pulmonary tissue to manganese dioxide.** *Toxicology* 1977, **8**:177-184.
17. Ulrich CE, Rinehart VV, Brandt M: **Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. III. Pulmonary function, electromyograms, limb tremor, and tissue manganese data.** *Am Ind Hyg Assoc J* 1979, **40**:349-353.
18. Zaidi SH, Dogra RK, Shanker R, Chandra SV: **Experimental infective manganese pneumoconiosis in guinea pigs.** *Environ Res* 1973, **6**:287-297.
19. Camner P, Curstedt T, Jarstrand C, Johannsson A, Robertson B, Wiernik A: **Rabbit lung after inhalation of manganese chloride: a comparison with the effects of chlorides of nickel, cadmium, cobalt, and copper.** *Environ Res* 1985, **38**:301-309.
20. Dorman DC, McManus BE, Parkinson CU, Manuel CA, McElveen AM, Everitt JL: **Nasal toxicity of manganese sulfate and manganese phosphate in young male rats following subchronic (13-week) inhalation exposure.** *Inhal Toxicol* 2004, **16**:481-488.
21. National Research Council: *Guide for the Care and Use of Laboratory Animals* Washington DC: National Academy Press; 1996.
22. Newland MC: **Animal models of manganese's neurotoxicity.** *Neurotoxicology* 1999, **20**:415-432.
23. Kepler GM, Richardson RB, Morgan KT, Kimbell JS: **Computer simulation of inspiratory nasal airflow and inhaled gas uptake in a rhesus monkey.** *Toxicol Appl Pharmacol* 1998, **150**:1-11.
24. Martonen TB, Katz IM, Musante CJ: **A nonhuman primate aerosol deposition model for toxicological and pharmaceutical studies.** *Inhal Toxicol* 2001, **13**:307-324.
25. Dorman DC, Struve MF, James RA, Marshall MW, Parkinson CU, Wong BA: **Influence of particle solubility on the delivery of inhaled manganese to the rat brain: manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure.** *Toxicol Appl Pharmacol* 2001, **170**:79-87.
26. Mellick PW, Dungworth DL, Schwartz LW, Tyler WS: **Short term morphologic effects of high ambient levels of ozone on lungs of rhesus monkeys.** *Lab Invest* 1977, **36**:82-90.
27. Dorman DC, McManus BE, Marshall MW, James RA, Struve MF: **Old age and gender influence the pharmacokinetics of inhaled manganese sulfate and manganese phosphate in rats.** *Toxicol Appl Pharmacol* 2004, **197**:113-124.
28. Brack M: **Histochemistry of the lung mite pigment in infections of *Pneumonyssus sp.* in nonhuman primates.** *Parasitology* 1972, **64**:47-52.
29. Hull WB: **Respiratory mite parasites in nonhuman primates.** *Lab Anim Care* 1970, **20**:402-406.
30. Fuller GN, Burger PC: **Central nervous system.** In *Histology for Pathologists* 2nd edition. Edited by: Sternberg SS. Philadelphia: Lippincott Williams & Wilkins; 1997:243-282.
31. Morgan KT, Johnson BP, Frith CH, Townsend J: **An ultrastructural study of spontaneous mineralization in the brains of aging mice.** *Acta Neuropathol* 1982, **58**:120-124.
32. Kast A, Peil H, Weisse I: **Calcified foci at the junction between adrenal cortex and medulla of rhesus monkeys.** *Lab Anim* 1994, **28**:80-89.
33. Wadsworth PF, Jones HB, Cavanagh JB: **The topography, structure and incidence of mineralized bodies in the basal ganglia of the brain of cynomolgus monkeys (*Macaca fascicularis*).** *Lab Anim* 1995, **29**:276-281.
34. Donaldson K, Tran CL: **Inflammation caused by particles and fibers.** *Inhal Toxicol* 2002, **14**:5-27.
35. Tyler NK, Plopper CG: **Morphology of the distal conducting airways in rhesus monkey lungs.** *Anat Rec* 1985, **211**:295-303.
36. Heppleston AG: **The pathological anatomy of simple pneumoconiosis in coal workers.** *J Pathol Bact* 1953, **66**:235-246.
37. Hyde DM, Hubbard WC, Wong V, Wu R, Pinkerton K, Plopper CG: **Ozone-induced acute tracheobronchial epithelial injury: relationship to granulocyte emigration in the lung.** *Am J Respir Cell Mol Biol* 1992, **6**:481-497.
38. Niewoehner DE, Kleinerman J, Rice DB: **Pathologic changes in the peripheral airways of young cigarette smokers.** *N Engl J Med* 1974, **291**:755-758.
39. Ryu JH, Myers JL, Swensen SJ: **Bronchiolar disorders.** *Am J Respir Crit Care Med* 2003, **168**:1277-1292.
40. Boobar MM, Goodarzi F: **A longitudinal follow-up of pulmonary function and respiratory symptoms in workers exposed to manganese.** *J Occup Environ Med* 2002, **44**:282-290.
41. Nikula KJ, Vallyathan V, Green FH, Hahn FF: **Influence of exposure concentration or dose on the distribution of particulate material in rat and human lungs.** *Environ Health Perspect* 2001, **109**:311-318.
42. Harmsen AG, Mason MJ, Muggenburg BA, Gillett NA, Jarpe MA, Bice DE: **Migration of neutrophils from lung to tracheobronchial lymph node.** *J Leukoc Biol* 1987, **41**:95-103.
43. Lee KP, Kelly DP: **Translocation of particle-laden alveolar macrophages and intra-alveolar granuloma formation in rats exposed to Ludox colloidal amorphous silica by inhalation.** *Toxicology* 1993, **77**:205-222.
44. Henderson RF, Driscoll KE, Harkema JR, Lindenschmidt RC, Chang IY, Maples KR, Barr EB: **A comparison of the inflammatory response of the lung to inhaled versus instilled particles in F344 rats.** *Fundam Appl Toxicol* 1995, **24**:183-197.
45. Hiramatsu K, Azuma A, Kudoh S, Desaki M, Takizawa H, Sugawara I: **Inhalation of diesel exhaust for three months affects major cytokine expression and induces bronchus-associated lymphoid tissue formation in murine lungs.** *Exp Lung Res* 2003, **29**:607-622.
46. Sato A, Chida K, Iwata M, Hayakawa H: **Study of bronchus-associated lymphoid tissue in patients with diffuse panbronchiolitis.** *Am Rev Respir Dis* 1992, **146**:473-478.
47. Suda T, Chida K, Hayakawa H, Imokawa S, Iwata M, Nakamura S, Sato A: **Development of bronchus-associated lymphoid tissue in chronic hypersensitivity pneumonitis.** *Chest* 1999, **115**:357-363.
48. Brenneman KA, Wong BA, Bucellato MA, Costa ER, Gross EA, Dorman DC: **Direct olfactory transport of inhaled manganese (<sup>54</sup>MnCl<sub>2</sub>) to the rat brain: Toxicokinetic investigations in a unilateral nasal occlusion model.** *Toxicol Appl Pharmacol* 2000, **169**:238-248.

49. Molders N, Schilling PJ, Wong J, Roos JW, Smith IL: **X-ray fluorescence mapping and micro-XANES spectroscopic characterization of exhaust particulates emitted from auto engines burning MMT-added gasoline.** *Environ Sci Technol* 2001, **35**:3122-3129.
50. Pellizzari ED, Clayton CA, Rodes C, Mason RE, Piper LL, Fort B, Pfeifer G, Lynam D: **Particulate matter and manganese exposures in Toronto, Canada.** *Atmos Environ* 1999, **33**:721-734.
51. Schlesinger RB: **Deposition and clearance of inhaled particles.** In *Concepts in Inhalation Toxicology* Edited by: McClellan RO, Henderson RF. Taylor and Francis, Washington, DC; 1995:191-224.
52. Asgharian B, Wood R, Schlesinger RB: **Empirical modeling of particle deposition in the alveolar region in the lungs: A basis for interspecies extrapolation.** *Fundam Appl Toxicol* 1995, **27**:232-238.
53. Snipes MB: **Long-term retention and clearance of particles inhaled by mammalian species.** *Crit Rev Toxicol* 1989, **20**:175-211.
54. Mercer RR, Crapo JD: **Structure of the gas exchange region of the lungs determined by three dimensional reconstruction.** In *Toxicology of the Lung* New York:Raven Press; 1988:43-70.
55. Tyler WS: **Small airways and terminal units: comparative subgross anatomy of lungs.** *Am Rev Respir Dis* 1983, **128**:S32-S36.
56. Hinds WC: *Aerosol Technology* 2nd edition. New York: John Wiley and Sons; 1999.

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## **ATTACHMENT B**

# **Summary of Relevant Toxicity Studies**

Current, Peer-reviewed Short-term Toxicity Data for Setting Guidance Levels

| Study                      | Type    | Mn Compound       | Particle Size (µm) | Exposure Type | Species Used in Study                                                            | Mn Exposure Concentration                 | Study/Exposure Details                                                                                                                                                                                                                                                                                                                                                                                                   | Primary Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Additional Observations                                                                                                                                                     | Comments                                                                                                                                                                                                                                                                                               |
|----------------------------|---------|-------------------|--------------------|---------------|----------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dorman et al. (2005)       | Primary | MnSO <sub>4</sub> | 1.72-2.12          | Whole body    | Male rhesus monkeys (4 or 6/group)                                               | 0 or 1.5 mg Mn/m <sup>3</sup>             | Subacute study: 6 hr/day, 5 days/wk, for 15 exposure days (90 hours total)                                                                                                                                                                                                                                                                                                                                               | Significant, mild subacute bronchiolitis, increase in bronchus-associated lymphoid tissue (BALT)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Histologic changes to the respiratory system & lung Mn concentrations were determined. No signs of clinical toxicity, including neurotoxicity, were observed in the animals | Based on this study, TCEQ identified 1.5 mg Mn/m <sup>3</sup> as a LOAEL for subacute exposure                                                                                                                                                                                                         |
|                            |         |                   |                    |               |                                                                                  |                                           | Subacute study: 6 hr/day, 5 days/wk, for 33 exposure days (198 hour total)                                                                                                                                                                                                                                                                                                                                               | Significant bronchiolitis impacting more of the respiratory bronchioles & alveolar duct inflammatory alterations & alveolar duct inflammation, as well as increased Mn lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                             | --                                                                                                                                                                                                                                                                                                     |
|                            |         |                   |                    |               | Male rhesus monkeys (4-6/group)                                                  | 0, 0.06, 0.3, or 1.5 mg Mn/m <sup>3</sup> | Subchronic study: 6 hours/day, 5 days/week, for 65 exposure days (390 hours total)                                                                                                                                                                                                                                                                                                                                       | Increased lung Mn concentrations in monkeys exposed to 0.3 or 1.5 mg Mn/m <sup>3</sup> for 65 days & alveolar duct inflammation, as well as increased                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                             | --                                                                                                                                                                                                                                                                                                     |
|                            |         |                   |                    |               | Male rhesus monkeys (8)                                                          | 1.5 mg Mn/m <sup>3</sup>                  | Subchronic study: 6 hours/day, 5 days/week, for 65 exposure days (390 hours total); plus 45 or 90 days for recovery                                                                                                                                                                                                                                                                                                      | Mn lung concentrations (seen at exposures for ≥15 days). However, all observed changes were reversible and not seen at 45 days post-exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                             | --                                                                                                                                                                                                                                                                                                     |
| McGough and Jardine (2017) | Primary | MnCl <sub>2</sub> | Not provided       | Nose-only     | Sprague Dawley rats (10/group/sex)                                               | 0, 2.2, 8.7 or 13.1 mg Mn/m <sup>3</sup>  | Initial range finding study; planned for 9 weeks but stopped at 3 weeks due to frank toxicity at 13.1 mg Mn/m <sup>3</sup>                                                                                                                                                                                                                                                                                               | Overt toxicity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | --                                                                                                                                                                          | --                                                                                                                                                                                                                                                                                                     |
|                            |         |                   | 2.32-2.57          |               | Sprague Dawley F0 and F1 rats (24-28 /sex/group); F2 rats (details not provided) | 0, 2.2, 4.4 or 8.7 mg Mn/m <sup>3</sup>   | 2-generation reproductive toxicity guideline study; F0 & F1: before mating (for 10 and 11 weeks, respectively), during mating, pregnancy and lactation (males: 6 hours/day, 7 days/week; 17 weeks [714 hours total]; females: no dose GD 20/21; 1 hour/day during days 1-2 of lactation; 2 hours/day during days 3-4 of lactation; 6 hours/day otherwise)<br><br>F2: exposed throughout gestation until lactation day 21 | No effects observed in the F2 rats; although mild respiratory effects occurred in the F0 rats at 4.4 & 8.8 mg Mn/m <sup>3</sup> . No reproductive effects occurred. The mild respiratory effects were attributed to irritation caused by Cl <sub>2</sub> and slower lung clearance of Mn+2                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                             | Although this study does not provide acute exposure data, it addresses one of the data gaps identified by ATSDR when it set the chronic MRL in 2012. Specifically, it supports the lack of reproductive & developmental toxicity at exposures higher than the subacute LOAEL from Dorman et al. (2005) |
| Saputra et al. (2016)      | Primary | MnCl <sub>2</sub> | 1.2                | Nose-only     | Male Sprague-Dawley rats (12/group)                                              | 0 or 17 mg Mn/m <sup>3</sup>              | 4 hours/day, 5 days/week for 3 weeks (60 hours total)                                                                                                                                                                                                                                                                                                                                                                    | Mild lung effects (minimal infiltration of inflammatory cells in respiratory bronchioles), altered expression of dopamine in the brain & significantly higher Mn levels in the striatum, cerebellum, prefrontal cortex, olfactory bulb, lung & other tissues                                                                                                                                                                                                                                                                                                                                                                                                                                      | The Mn-exposed group had no motor effects, no brain histopathological changes, no brain neuronal changes & no body weight differences                                       | LOAEL from this study was 17 mg/m <sup>3</sup>                                                                                                                                                                                                                                                         |
| HaMai et al. (2006)        | Primary | MnSO <sub>4</sub> | 0.55               | Nose-only     | Sprague-Dawley rats (3-5/group)                                                  | 0 or 0.71 mg Mn/m <sup>3</sup>            | Prenatal group: exposed pregnant females 2 hours/day on GDs 9 & 10 (4 hours total)<br><br>Adulthood group: exposed 2 hours/day starting at 6 weeks after birth for 10 days (20 hours total)<br><br>Prenatal + Adulthood group: exposed 2 hours/day on GDs 9 & 10, & 6 weeks of age for 10 days (24 hours total)                                                                                                          | While no overt toxicity was observed, in the Adult group, mRNA levels of amyloid precursor protein (APP), cyclooxygenase-2 (COX-2), neuronal nitric oxide synthase (nNOS), glial fibrillary acidic protein (GFAP), & transformation growth factor beta (TGF-β) were significantly decreased<br><br>The other two groups showed lesser decreases in mRNA levels for these genes. Animals in the Prenatal group had significant decreases in mRNA levels of all but TGF-β; rats in the Prenatal + Adult group had significant decreases in mRNA levels of COX-2, nNOS & TGF-β                                                                                                                       | Overall, brief Mn prenatal exposure to Mn lessened the response of several genes associated with inflammation or oxidative stress to additional Mn exposure                 | Subacute exposure to 0.71 mg Mn/m <sup>3</sup> during gestation and adulthood altered the transcription of certain genes, but did not result in biologically adverse effects. ATSDR considers these results as a NOAEL                                                                                 |
| Erikson et al. (2005)      | Primary | MnSO <sub>4</sub> | 1.03-1.07          | Whole body    | CD rats (10 rats/group/sex)                                                      | 0, 0.05, 0.5, or 1 mg Mn/m <sup>3</sup>   | Exposed 28 days before breeding & ≤14 days during mating (F0 generation) (7 days/week, 6 hours/day; up to 252 total hours)<br><br>Pregnant females exposed GD 0-GD 19, but not when delivery was anticipated (after GD 19)<br><br>Pups & nursing dams exposed to MnSO <sub>4</sub> during PND 1-PND 18 (222 total hours)<br><br>Animals allowed 3 weeks of recovery                                                      | Oxidative stress measurements were determined in 5 brain regions. While total glutathione (GSH) levels were unchanged, GSH levels were significantly lower in the cerebella of F1 males<br><br>At the highest concentration (1 mg Mn/m <sup>3</sup> ), glutamine synthetase (GS) mRNA was decreased in F1 female striata & increased in F1 male olfactory bulb and hypothalamus. Metallothionein (MT) was unchanged at 1 mg Mn/m <sup>3</sup> , 0.5 mg Mn/m <sup>3</sup> led to decreased MT in F1 female olfactory bulbs and F1 male hypothalamus & hippocampi<br><br>At the lowest dose (0.05 mg Mn/m <sup>3</sup> ) F1 males had decreased MT mRNA in the striatum, hippocampus & hypothalamus |                                                                                                                                                                             | Upon subchronic exposure to 0.05-1 mg Mn/m <sup>3</sup> , changes in biomarkers of oxidative stress following in utero & neonatal inhalation exposure to manganese persisted even after 3 weeks of recovery, although brain Mn levels returned to normal                                               |



Current, Peer-reviewed Short-term Toxicity Data for Setting Guidance Levels

| Study                | Type                                                                                                                 | Mn Compound                                                                  | Particle Size (µm) | Exposure Type | Species Used in Study                                         | Mn Exposure Concentration                                                                                                                                                                        | Study/Exposure Details                                                             | Primary Endpoints                                                                                                                                                     | Additional Observations | Comments                                                                                                                                                                                          |
|----------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------|---------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Taylor et al. (2006) | Review (evaluated 7 studies: Erikson et al. 2004, 2005, 2006; Dorman et al. 2001, 2004, 2005a; & Dobson et al. 2003) | MnSO <sub>4</sub> for 6 studies; manganese phosphate in Dorman et al. (2001) | Not provided       | Not provided  | Neonatal & adult rats (males & females) & male senescent rats | Across the studies, rats were exposed for 14 to 90 days, PND 19 or 45 (following exposure during gestation & lactation until PND 18), at concentrations ranging from 0.01–3 mg Mn/m <sup>3</sup> | Concentrations used were considered sufficient to cause Mn to accumulate in tissue | Measurements of oxidative stress included alterations in total GSH, MT mRNA, GS protein & RNA in the hypothalamus, hippocampus, striatum, olfactory bulb & cerebellum |                         | Oxidative stress does not appear to be a substantial component of Mn-induced neurotoxicity, & although there is evidence of oxidative stress in some areas of the brain, evidence is inconsistent |

**ATTACHMENT C**

**Schroeter et al. (2012)  
and Gentry et al. (2017)**

# Application of a Multi-Route Physiologically Based Pharmacokinetic Model for Manganese to Evaluate Dose-Dependent Neurological Effects in Monkeys

Jeffrey D. Schroeter,<sup>\*,1</sup> David C. Dorman,<sup>†</sup> Miyoung Yoon,<sup>\*</sup> Andy Nong,<sup>\*</sup> Michael D. Taylor,<sup>‡</sup> Melvin E. Andersen,<sup>\*</sup> and Harvey J. Clewell III<sup>\*</sup>

<sup>\*</sup>The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina; <sup>†</sup>College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina; and <sup>‡</sup>Afton Chemical Corp., Richmond, Virginia

<sup>1</sup>To whom correspondence should be addressed at Applied Research Associates, Inc., 8537 Six Forks Road, Suite 600, Raleigh, NC 27615. Fax: (919) 582-3301. E-mail: jschroeter@ara.com.

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Manganese (Mn) is an essential element that is neurotoxic under certain exposure conditions. Monkeys and humans exposed to Mn develop similar neurological effects; thus, an improved understanding of the dose-response relationship seen in nonhuman primates could inform the human health risk assessment for this essential metal. A previous analysis of this dose-response relationship in experimental animals (Gwiazda, R., Lucchini, R., and Smith, D., 2007, Adequacy and consistency of animal studies to evaluate the neurotoxicity of chronic low-level manganese exposure in humans, *J. Toxicol. Environ. Health Part A* **70**, 594–605.) relied on estimates of cumulative intake of Mn as the sole measure for comparison across studies with different doses, durations, and exposure routes. In this study, a physiologically based pharmacokinetic model that accurately accounts for the dose dependencies of Mn distribution was used to estimate increases in brain Mn concentrations in monkeys following Mn exposure. Experimental studies evaluated in the analysis included exposures by inhalation, oral, iv, ip, and sc dose routes, and spanned durations ranging from several weeks to over 2 years. This analysis confirms that the dose-response relationship for the neurotoxic effects of Mn in monkeys is independent of exposure route and supports the use of target tissue Mn concentration or cumulative target tissue Mn as the appropriate dose metric for these comparisons. These results also provide strong evidence of a dose-dependent transition in the mode of action for the neurological effects of Mn that needs to be considered in risk assessments for this essential metal.

**Key Words:** manganese; neurotoxicity; dose response; physiologically based pharmacokinetic modeling.

Manganese (Mn) is an essential nutrient that is required for many physiological functions. Mn occurs naturally in soil, water, and air, leading to a widespread presence in the environment. The primary source of Mn exposure is through the diet.

Adult dietary intake in people has been estimated to range from 1 to 10 mg Mn/day with only a small fraction (1–5%) absorbed by the gastrointestinal (GI) tract (Aschner *et al.*, 2005; ATSDR, 2000). Homeostatic controls regulate intestinal absorption and biliary excretion to ensure adequate and stable tissue Mn concentrations and to prevent Mn deficiency or toxicity despite mild fluctuations in daily exposure levels.

As with other essential elements, Mn may induce toxicity under certain high-dose exposure conditions. Adverse neurological, reproductive, and respiratory effects characterize Mn toxicity in humans. Mn-induced neurotoxicity is of particular concern and is considered one of the most sensitive endpoints (Aschner *et al.*, 2005). Early manifestations of Mn overexposure include fatigue, headache, muscle cramps, loss of appetite, apathy, insomnia, and diminished libido. As overexposure continues and the disease progresses, patients may develop prolonged muscle contractions (dystonia), decreased muscle movement (hypokinesia), rigidity, and muscle tremors (Pal *et al.*, 1999). Structural changes in the globus pallidus of Mn-exposed people indicate that this brain region is a target site for Mn accumulation and effects (Perl and Olanow, 2007). Individuals with chronic Mn neurotoxicity resemble patients with Parkinson's disease; however, unlike in Parkinson's disease, the substantia nigra is largely spared and dopamine levels remain generally unaffected during Mn neurotoxicity (Guilarte, 2010).

Mn-induced neurological effects have been reported from studies of occupational exposure to high inhaled (> 0.2 mg/m<sup>3</sup>) Mn concentrations (Myers *et al.*, 2003; Roels *et al.*, 1987), environmental studies of residents near ferroalloy plants (Lucchini *et al.*, 2007), individuals exposed to Mn-laden drinking water (Bouchard *et al.*, 2011; Kawamura *et al.*, 1941; Kondakis *et al.*, 1989), and from people with prolonged use of total parenteral nutrition formulations that contain Mn

(Alves *et al.*, 1997; Fell *et al.*, 1996). These observations suggest that brain Mn concentration is the critical determinant for Mn neurotoxicity, regardless of exposure route. This is an important distinction to consider when assessing long-term health risks from chronic, low-level environmental Mn exposure.

Studies on Mn neurotoxicity have been conducted in rodents and nonhuman primates using various exposure routes and a wide range of doses and durations. Gwiazda *et al.* (2007) conducted a review of subchronic to chronic rodent and nonhuman primate studies to determine whether a consistent dose-response relationship existed among different studies. One goal of Gwiazda *et al.*'s work was to determine whether animal studies could be used to evaluate the neurotoxicity of chronic low-level Mn exposures in humans. They estimated internal cumulative Mn dose as "the total amount of Mn that was taken up into the circulatory system by the time the endpoint was detected." The range of exposures associated with adverse changes was profound (over two orders of magnitude) in the animal studies evaluated by Gwiazda *et al.*, leading them to conclude that most existing animal studies might be of limited relevance for the risk assessment of chronic low-level Mn exposure to humans.

Since Gwiazda *et al.*'s study was published, several physiologically based pharmacokinetic (PBPK) models for Mn have been reported (Nong *et al.*, 2009; Schroeter *et al.*, 2011; Yoon *et al.*, 2011). These PBPK models effectively simulate Mn tissue kinetics from inhaled, oral, and parenteral Mn intake (Andersen *et al.*, 2010). This multi-dose route capability is achieved by incorporating homeostatic control processes, saturable tissue binding capacities, and preferential fluxes in various tissue regions (see Taylor *et al.*, 2012 for review). PBPK models have been widely used in risk assessment of chemical compounds to support extrapolation across species, high to low doses, and across exposure routes and to allow for calculation of target tissue dose, which is more biologically relevant than administered dose, exposure concentration, or estimated systemic dose as a metric for predicting toxic outcomes.

The purpose of this study was to apply PBPK modeling approaches to a subset of the studies initially identified by Gwiazda *et al.* (2007). We focused our attention on work performed in nonhuman primates because unlike rodents, Mn-exposed monkeys develop regionally selective increases in brain Mn concentrations (Aschner *et al.*, 2005; Dorman *et al.*, 2006b; Eriksson *et al.*, 1992b; Newland *et al.*, 1989) and behavioral effects similar to those seen in Mn-affected humans (Olanow *et al.*, 1996). To this end, we used a PBPK model developed specifically for rhesus monkeys (Schroeter *et al.*, 2011) to simulate the exposure scenarios from each study and to predict the corresponding increases in brain Mn concentrations for various dose routes, exposure concentrations, and durations.

## MATERIALS AND METHODS

### Study Selection

The 15 nonhuman primate studies identified by Gwiazda *et al.* (2007) were used as a starting point for this analysis. Three of the studies identified by Gwiazda used cebus monkeys (*Cebus spp.*) or squirrel monkeys (*Saimiri sciureus*) (Neff *et al.*, 1969; Newland and Weiss, 1992; Ulrich *et al.*, 1979). These studies were excluded from our analysis because the PBPK models were developed and calibrated using pharmacokinetic data obtained in rhesus monkeys (*Macaca mulatta*) or phylogenetically similar macaque relatives. A fourth excluded study (Van Bogaert and Dallemagne, 1946) used macaques but included an inhalation coexposure to sodium perchlorate, thus confounding our interpretation of the reported clinical signs. In addition to the studies identified by Gwiazda, we also included two recent studies (Dorman *et al.*, 2006a; Guilarte *et al.*, 2006) and the report by Coulston and Griffin (1976). The study by Chandra *et al.* (1979) was also included for model calibration although clinical effects were not reported. In the end, 15 studies were identified in our analysis (summarized in Table 1). Exposure routes for these studies included inhalation, oral delivery, and iv, ip, sc, and im injection. Different forms of Mn were used in the exposures and included both soluble (e.g.,  $\text{MnCl}_2$  and  $\text{MnSO}_4$ ) and relatively insoluble (e.g.,  $\text{MnO}_2$  and  $\text{Mn}_3\text{O}_4$ ) forms of Mn. These studies also included a wide range of Mn dose levels, dose frequencies, and exposure durations.

### Assessment of Clinical Signs

Clinical signs were evaluated using modifications of clinical sign scales developed for monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism (Imbert *et al.*, 2000; Kurlan *et al.*, 1991). Evaluations were based upon the original data and descriptions as published in the studies included in this review (Table 1). Scoring of clinical signs was performed by a veterinarian with expertise in neurotoxicology (David D. Dorman). The following effect categories and severity scoring system were used to assess the monkey studies:

- Coordination
  - 0—normal
  - 1—very slight to no loss of balance
  - 2—moderate lapses in balance
  - 3—frequent and major lapses in balance
- Bradykinesia
  - 0—normal speed and facility of movement
  - 1—mild (25–50%) reduction
  - 2—moderate (51–75%) reduction
  - 3—severe (> 75%) reduction
- Rigidity/Gait disorders
  - 0—normal
  - 1—walks slowly and with difficulty
  - 2—markedly impaired; ambulate slowly +/- effort
  - 3—severe decrease in ability to ambulate
- Postural instability
  - 0—absent
  - 1—minor
  - 2—marked
- Muscle tremors
  - 0—absent
  - 1—mild
  - 2—moderate
  - 3—severe
- Other neurological clinical signs (included CNS excitation and hyperactivity)
  - 0—none
  - 1—mild
  - 2—moderate
  - 3—severe

TABLE 1  
Summary of Mn Exposure Studies in Rhesus Monkeys

| Study                                                        | Mn form                        | Dose route | Body weight (kg) | Dosing regimen                                                                                                                                           |
|--------------------------------------------------------------|--------------------------------|------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chandra <i>et al.</i> (1979)                                 | MnCl <sub>2</sub>              | oral       | 5                | 5.6 mg/kg Mn in MnCl <sub>2</sub> solution given once daily for 18 months                                                                                |
| Gupta <i>et al.</i> (1980)                                   | MnCl <sub>2</sub>              | oral       | 5–6              | 7.0 mg/kg Mn in MnCl <sub>2</sub> solution given once daily for 18 months                                                                                |
| Van Bogaert and Dallemagne (1946)                            | MnSO <sub>4</sub>              | oral       | 2.85             | 1.3–6.3 mg/kg Mn in MnSO <sub>4</sub> solution given once daily for 292 days                                                                             |
| Mella (1924)                                                 | MnCl <sub>2</sub>              | ip         | 5 <sup>a</sup>   | 0.5–2.2 mg/kg Mn given every other day for up to 14 months                                                                                               |
| Olanow <i>et al.</i> (1996)                                  | MnCl <sub>2</sub>              | iv         | 12–18            | 2.8–4.0 mg/kg Mn given by iv injection 7 times at ~1-week intervals                                                                                      |
| Guilarte <i>et al.</i> (2006)/Schneider <i>et al.</i> (2006) | MnSO <sub>4</sub>              | iv         | 6.5              | 3.6–5.4 mg/kg Mn injected weekly for approximately 40 weeks                                                                                              |
| Suzuki <i>et al.</i> (1975)                                  | MnO <sub>2</sub>               | sc         | 3.5–4.5          | Up to 158 mg/kg Mn injected once a week for 9 weeks                                                                                                      |
| Eriksson <i>et al.</i> (1987)                                | MnO <sub>2</sub>               | sc         | 3.5–4.5          | Approximately 112 mg/kg Mn injected on 18 occasions over 5 months                                                                                        |
| Eriksson <i>et al.</i> (1992a)                               | MnO <sub>2</sub>               | sc         | 4.5–6.0          | 38 mg/kg Mn injected on 13 occasions over 26 months                                                                                                      |
| Eriksson <i>et al.</i> (1992b)                               | MnO <sub>2</sub>               | sc         | 4–5              | 89 mg/kg Mn injected on 11 occasions over 4 months                                                                                                       |
| Pentschew <i>et al.</i> (1963)                               | MnO <sub>2</sub>               | im         | 5 <sup>a</sup>   | Single doses of 252 and 441 mg/kg Mn injected 2 months apart                                                                                             |
| Bird <i>et al.</i> (1984)                                    | MnO <sub>2</sub>               | inhalation | 2–3              | Exposure to 30 mg Mn/m <sup>3</sup> for 6 h/day, 5 days/week for 2 years                                                                                 |
| Nishiyama <i>et al.</i> (1977)                               | MnO <sub>2</sub>               | inhalation | 3–4              | Exposure to 0.7 or 3.0 mg Mn/m <sup>3</sup> for 22 h/day, 7 days/week for 10 months                                                                      |
| Coulston and Griffin (1976)                                  | Mn <sub>3</sub> O <sub>4</sub> | inhalation | 2.75–6.5         | Exposure to 0.1 mg Mn/m <sup>3</sup> for 23 h/day, 7 days/week for up to 15 months or to 5.0 mg Mn/m <sup>3</sup> for 23 h/day, 7 days/week for 23 weeks |
| Dorman <i>et al.</i> (2006)                                  | MnSO <sub>4</sub>              | inhalation | 2.5              | Exposure to 0.06, 0.3, or 1.5 mg Mn/m <sup>3</sup> for 6 h/day, 5 days/week for 90 days                                                                  |

<sup>a</sup>Body weights were not reported in the study, so a 5 kg body weight for an adult rhesus monkey was assumed for model simulations.

The severity scores for the categories listed above were summed to obtain a final severity score for each dose group in the studies listed in Table 1. The minimum possible score was 0 (no effect) and the maximum possible score was 17. If a sufficient description of a change in clinical signs was reported during the course of the exposure, then severity scores at multiple time points were used in the analysis.

Mn PBPK Model

The Mn PBPK model for rhesus monkeys was previously described in detail (Nong *et al.*, 2009; Schroeter *et al.*, 2011), so only a brief description is given of some of the important aspects of the model. The PBPK model contained compartments for the liver, lung, nasal cavity, bone, blood, and brain regions (Fig. 1). All other body tissues were combined into a single compartment. The brain was divided into compartments representing blood, globus pallidus, cerebellum, olfactory bulb, and pituitary gland. The globus pallidus, cerebellum, and pituitary gland were included because they accumulate Mn to varying degrees during inhalation exposure. The olfactory bulb was included because it receives direct transport from olfactory epithelium during Mn inhalation (Aschner *et al.*, 2005; Dorman *et al.*, 2006a,b).

Tissue Mn concentrations represent the sum of free Mn and bound forms within the tissues. Free Mn circulates in the blood throughout the body; the bound form is stored in tissue constituents. Tissue binding is a reversible, saturable process that likely represents incorporation of specific macromolecular Mn stores. The incorporation of Mn into tissue constituents is governed by tissue-specific association and dissociation rate constants ( $k_a$  and  $k_d$ ). The distribution between bound and free Mn is determined by the dissociation binding ratio ( $k_d/k_a$ ) and the tissue-specific maximum binding capacity ( $B_{max}$ ), which regulates the storage capacity of bound Mn in each tissue. Saturation of the binding capacity with increased exposure leads to increases in free Mn and subsequent increases in total tissue Mn. Following cessation of exposure, free Mn is rapidly cleared from the body and tissue Mn concentrations return to their basal levels.

The differential rise in free Mn concentration in brain regions was described with tissue-specific diffusion rate constants ( $k_{in}$  and  $k_{out}$ ) to describe diffusion-limited flux between brain blood and brain tissues. The influx rates for the globus pallidus and pituitary regions were dose dependent in order to

accurately describe changes in Mn concentration in these brain regions with increased Mn exposure. Increases in free Mn concentration in brain regions depend on asymmetric diffusional clearance rates, binding rate constants, and the binding capacity of each tissue. Tissue Mn binding capacity and diffusion parameters were calibrated by Schroeter *et al.* (2011) to the pharmacokinetic data from Mn-exposed monkeys in Dorman *et al.* (2006a) to simulate the rise in tissue Mn levels following the onset of inhalation exposure, followed by a return to basal levels after the exposure period. These parameters were unchanged for all simulations in this study.

A series of gut compartments were included in the PBPK model to track Mn absorption by the GI tract (Fig. 1). For dietary Mn, a small fraction ( $F_{dietup}$ ) was absorbed by the GI tract and directed to the liver for systemic circulation. The remaining fraction of Mn in the gut lumen ( $1 - F_{dietup}$ ) was either transiently stored in gut epithelial cells ( $F_{ent}$ ) or transferred to the lower GI tract lumen ( $1 - F_{ent}$ ) and excreted through the feces. Mn transfer from the gut lumen to the portal blood was reflected by the rate constant  $k_{gr}$ . Mn transfer from the gut epithelium to the lower GI tract occurred by sloughing of enterocytes from the epithelial layer ( $k_{ent}$ ). The stored Mn in enterocytes was not available to the systemic circulation due to rapid enterocyte turnover and was excreted into feces.

The elimination of Mn from the body occurs via biliary excretion in the liver. Biliary excretion was governed by the rate constant,  $k_{bile}$ , which was induced by blood concentration to reflect the dose-dependent behavior of Mn elimination (Nong *et al.*, 2009):

$$k_{bile} = k_{bile0} \cdot \left( 1 + \frac{k_{bmax} \cdot C_{art}^n}{k_{b50}^n + C_{art}^n} \right),$$

where  $k_{bile0}$  is the basal biliary excretion rate constant,  $k_{bmax}$  is the maximal increase in the excretion rate constant,  $k_{b50}$  is the arterial concentration at half the induced level of Mn in the arterial blood ( $C_{art}$ ), and  $n$  is the slope factor. Arterial blood concentration ( $C_{art}$ ) was used as a surrogate for free liver Mn concentration because Mn blood levels were directly measured in exposed monkeys (Dorman *et al.*, 2006a).

As described in Schroeter *et al.* (2011), fractional dietary absorption ( $F_{dietup} = 0.0021$ ) and the biliary excretion rate constant ( $k_{bilec} = 0.051$ ) were calibrated by fitting basal Mn tissue concentrations to tissue levels from the

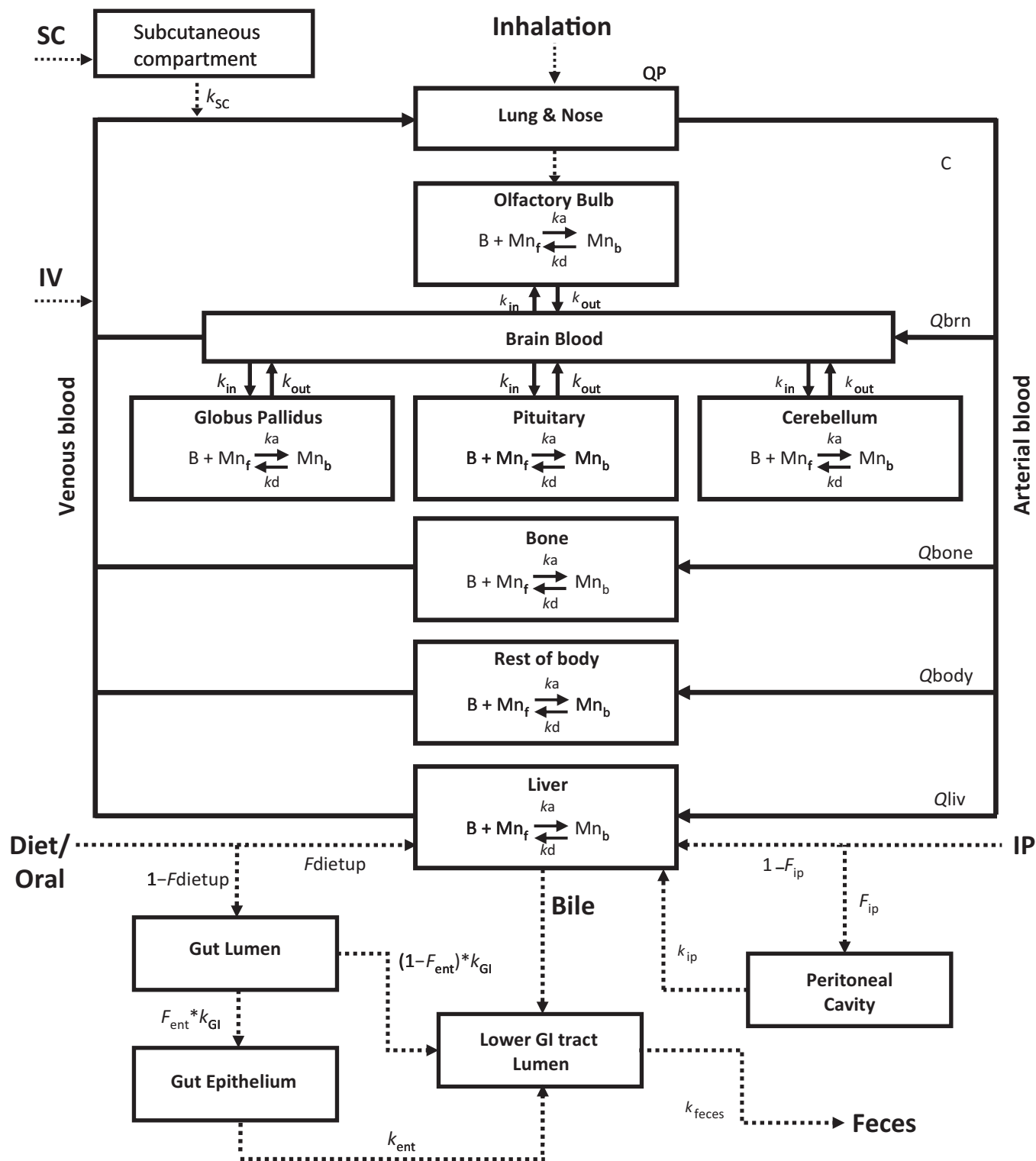


**FIG. 1.** Schematic of the Mn PBPK model for nonhuman primates. The PBPK model can accommodate the following Mn exposure routes: inhalation, diet/oral, ip, iv, and sc. Tissue-specific binding processes were controlled by association and dissociation parameters ( $k_a$  and  $k_d$ ) and the binding capacity ( $B_{tissue}$ ). Diffusion rate constants ( $k_{in}$  and  $k_{out}$ ) control increases in free Mn in brain regions.  $Q_{tissue}$  parameters refer to tissue blood flow rates.



control monkeys in Dorman *et al.* (2006a). Parameters governing GI absorption of Mn were calibrated using clearance data of oral doses of  $^{54}\text{Mn}$  (Furchner *et al.*, 1966). Biliary induction parameters were originally estimated by Nong *et al.* (2009) for low-dose Mn inhalation exposures (Dorman *et al.*, 2006a), where a maximum induction factor of  $k_{\text{bmax}} = 2.5$  was sufficient to describe the increase in biliary excretion following Mn exposure. However, most of the studies that were considered in this analysis used much higher Mn doses, so a larger maximal induction factor was needed to simulate increased biliary excretion rates following increased Mn intake. For all of the simulations in this study, the parameter  $k_{\text{bmax}}$  was increased to 20.0 and the other parameters in the biliary induction equation were modified accordingly ( $k_{\text{b50}} = 0.105$ ,  $n = 2.1$ ) to remain consistent with the low-dose behavior described by Nong *et al.* (2009). Studies in rats have shown that the biliary excretion of Mn is saturable, indicating a carrier-mediated transport mechanism (Ballatori *et al.*, 1987; Klaassen, 1974). To date, the transport protein(s) responsible for transporting Mn from hepatocytes into bile remain unknown. Because of known interaction between Mn and iron, it is plausible that Mn may share iron efflux transporters including ferroportin (Fpn1/Slc40a1), divalent metal transporter-1 (DMT-1), or copper ATPase (Atp7a or Atp7b) (Abboud and Haile, 2000; Goss *et al.*, 2008). The eightfold increase in  $k_{\text{bmax}}$  is consistent with studies evaluating Atp7a and DMT-1 hepatic expression in a rodent model of iron deficiency (which mimics Mn toxicity) (Jiang *et al.*, 2011).

#### Simulation of Mn Exposure Routes

The Mn PBPK model included the exposure routes that have been used in experimental studies (Table 1). For all exposures, the nominal dose used in modeling simulations was calculated from the Mn atomic weight fraction in the administered solution (or exposure concentration). Typical commercial diets provided to research monkeys contain 70 to 100 ppm Mn (Knapka *et al.*, 1995). All simulations were, therefore, conducted with monkeys maintained on an 80 ppm diet, simulated as a continuous dietary exposure. The one exception was the study by Dorman *et al.* (2006a), in which a 133 ppm diet was specified. Simulated exposures followed the dosing schedules precisely as described in the studies (e.g., dosing every day, every other day, once a week, etc.). All model parameters governing internal Mn kinetics, such as diffusion constants, biliary induction parameters, and GI absorption constants, remained unchanged for all of the simulations in this study, regardless of exposure route.

**Oral exposure.** Oral Mn exposures were given once daily in either  $\text{MnCl}_2$  or  $\text{MnSO}_4$  solutions (Chandra *et al.*, 1979; Gupta *et al.*, 1980; Van Bogaert and Dallemagne, 1946). For PBPK model simulations, these exposures were treated as a daily bolus dose and intestinal absorption was modeled in the same way as dietary Mn exposure. Even though GI absorption of Mn may decrease with time in reaction to increased oral dosage levels, uncertainties surrounding the timing and magnitude of this change led us to keep  $F_{\text{dietup}}$  constant. This decision also reflected the desire to maintain the most conservative scenario by assuming that  $F_{\text{dietup}}$  did not decrease with increased Mn oral doses.

**Intraperitoneal injection.** Following the dosing schedule given by Mella (1924), which was the only study in this analysis to use the ip route, injections of  $\text{MnCl}_2$  solution were given every other day with gradually increased dosage levels. Injection of Mn solution by the ip route was simulated by assuming that the majority of the ip dose was directly absorbed in the liver and a small fraction ( $F_{\text{ip}}$ ) was absorbed into the peritoneal cavity for slow release into the liver (Fig. 1). The rate constant  $k_{\text{ip}}$  governs the movement of Mn from the peritoneal cavity to the liver. The parameters  $F_{\text{ip}} = 0.03$  and  $k_{\text{ip}} = 1.0 \times 10^{-7} \text{ h}^{-1}$  were previously calibrated to the whole-body elimination data of  $^{54}\text{Mn}$  given by ip injection (Dastur *et al.*, 1971), as described by Schroeter *et al.* (2011). These parameters were unchanged for simulations of the Mella study.

**Intravenous injection.** Dosing for iv studies was typically once per week (Guilarte *et al.*, 2006; Olanow *et al.*, 1996) although longer durations between injections were sometimes needed depending on the state of the animal. For model simulations, the iv dose was input directly into venous blood (Fig. 1).

**sc injection.** Studies on sc administration used  $\text{MnO}_2$  powder mixed with saline, olive oil, or water for injection into sc tissue (Eriksson *et al.*, 1987, 1992a,b; Suzuki *et al.*, 1975). For model simulations, the entire Mn dose from the sc injection went into a compartment representing sc tissue (Fig. 1). Mn delivery by im injection (Pentschew *et al.*, 1963) was treated the same as a sc injection. The rate constant  $k_{\text{sc}} = 0.0007 \text{ h}^{-1}$ , which governs the release of Mn from the sc tissue into the venous blood, and the bioavailability of  $\text{MnO}_2$  at the injection site (42%) were calibrated by fitting model predictions of globus pallidus Mn concentrations to the data from Suzuki *et al.* (1975) and Eriksson *et al.* (1987), where globus pallidus Mn concentrations were measured at multiple time points following sc Mn injections. These model parameters were kept constant for all sc exposure simulations.

**Inhalation exposure.** Inhalation exposures were simulated using the exposure concentrations and schedules (e.g., days/week, hours/day) used in the experimental procedures (Bird *et al.*, 1984; Coulston and Griffin, 1976; Dorman *et al.*, 2006a; Nishiyama *et al.*, 1977). Respiratory tract deposition was estimated for inhalation of  $\text{MnSO}_4$  particles with a mass median aerodynamic diameter of 2.0  $\mu\text{m}$ , a geometric SD of 1.5 and a particle density of 2.95  $\text{g/cm}^3$  (Dorman *et al.*, 2006a). Lung and nasal deposition efficiencies for these aerosol particles were estimated to be 40 and 27%, respectively (Schroeter *et al.*, 2011). No distinction was made between deposition on tracheobronchial or pulmonary airways due to uncertainties regarding clearance and absorption rates from these lung regions. Nasal deposition was further partitioned onto respiratory and olfactory epithelium according to an airflow allocation of 91 and 9%, respectively (Kepler *et al.*, 1998). For model simulations of the Dorman study, deposited Mn from  $\text{MnSO}_4$  particles was rapidly absorbed from lung tissues and nasal respiratory epithelium into the systemic circulation or transported from nasal olfactory epithelium to the olfactory bulb. For simulations of other studies that used  $\text{MnO}_2$  and  $\text{Mn}_3\text{O}_4$  (Bird *et al.*, 1984; Coulston and Griffin, 1976; Nishiyama *et al.*, 1977), lung deposition was decreased to account for different particle size fractions and reduced bioavailability of less soluble Mn forms in lung tissues (Table 3).

#### Dose Metrics

PBPK model simulations were run from the beginning of the exposure period (time = 0) until exposures stopped or clinical outcomes were observed (time =  $T$ ), as reported in each study. Simulations were run using AcsIX version 3.0 (Aegis Technologies Group, Inc., Huntsville, AL). For each simulation, time-course profiles of tissue Mn concentrations following Mn exposure were evaluated. Mn concentrations in the globus pallidus were considered for the dose-response analysis because it is the likely target tissue for Mn-induced motor effects and is a conservative surrogate for other potential target brain regions that do not accumulate Mn as readily. The following three dose metrics for globus pallidus Mn concentration ( $C_{\text{gp}}(t)$ ) were used to correlate with observed clinical effects in monkeys:

$$\text{Peak concentration} = \max \{C_{\text{gp}}(t)\}_{t=0,T}$$

$$\text{Area under the curve (AUC)} = \int_0^T C_{\text{gp}}(t) dt$$

$$\text{Average concentration} = \frac{1}{T} \cdot \int_0^T C_{\text{gp}}(t) dt$$

#### Categorical Regression

A regression analysis was performed using the U.S. EPA CatReg software (available for download at [www.epa.gov/ncea](http://www.epa.gov/ncea)). CatReg fits a cumulative probability distribution using the method of maximum likelihood estimation to estimate the probability of a specific severity level (i.e., a category) at any specified dose. The dose can be defined using any relevant dose metric. The dose-response behavior was evaluated by plotting the severity scores for each dose group from the Mn exposure studies versus the corresponding dose metrics of peak concentration, average concentration, and AUC in the globus pallidus from the PBPK model simulations.

## RESULTS

### *Clinical Observations*

In general, studies performed prior to the 1990s had limited histological, neurochemical, or neuropathological assessments. These studies generally relied on very high-dose Mn exposures, and monkeys often developed postural instability, increased excitability, hypoactivity, falling, muscular rigidity, intention and/or action tremors, and ataxia. Studies using lower Mn doses were often associated with hypoactivity, loss of fine motor control, action tremor, or deficits in working memory. The severity scores applied to each dose group in each of the studies are shown in Table 2. Using this scoring system, the maximum summed severity score in this analysis was 9. With the exception of the inhalation exposures, most studies either used one monkey in each dose group or reported effects for individual monkeys.

### *PBPK Model Simulations*

Three studies used the oral route to deliver a Mn solution given as a bolus dose once daily. In the study by Chandra *et al.* (1979), brain Mn concentrations were reported in monkeys following an 18-month exposure period. Increases of 173 and 24% above control levels were reported in the midbrain region and cerebellum, respectively. Model predictions for this scenario yielded maximum tissue Mn concentrations of 138 and 57% for the globus pallidus and cerebellum, respectively. The study by Gupta *et al.* (1980) used an identical exposure scenario except that slightly higher Mn doses were used (7.0 vs. 5.6 mg/kg in Chandra *et al.* (1979)) and clinical observations were reported at the end of the exposure period. In the study by Van Bogaert and Dallemagne (1946), oral doses were also administered daily but were varied during the exposure period. The PBPK model simulation of this exposure is shown in Figure 2. Globus pallidus Mn concentrations were observed to fluctuate with the daily dosing regimen and also increased with higher Mn doses. A maximum globus pallidus concentration of 1.5  $\mu\text{g/g}$  was predicted at the highest oral dose of 6.3 mg/kg. Although the oral doses were high in these studies, only a small fraction was predicted to be absorbed into the systemic circulation from the GI tract, resulting in moderate increases in brain Mn concentrations.

In the study by Mella (1924), monkeys were injected by the ip route every other day with progressively higher Mn doses. The predicted globus pallidus Mn concentration for monkey no. 6 from Mella (1924) is shown in Figure 3. The initial ip dose of Mn was 0.9 mg/kg and continued for 96 days, followed by doses of 1.8 mg/kg for 48 days and 2.2 mg/kg for 22 days. The maximum predicted globus pallidus Mn concentration of 31.5  $\mu\text{g/g}$  occurred during the highest dosing period. Predicted brain Mn concentrations exhibited a wide fluctuation between doses due to rapid systemic delivery from ip injection. This was followed by rapid clearance of Mn from the body after the ip injection.

Simulation of Mn globus pallidus concentration following exposure by iv injection is shown in Figure 4. In this exposure (monkey no. 2 in Olanow *et al.*, 1996), the monkey was injected once per week with variable Mn doses of 2.8–3.6 mg/kg. Extremely high brain Mn concentrations (> 50  $\mu\text{g/g}$ ) were predicted due to the high Mn doses and rapid delivery to tissues following direct systemic exposure from iv injection. These rapid increases in tissue Mn concentrations were followed by returns to near basal levels after several days. Similar behavior was observed in the other exposed monkeys from the Olanow study and in the iv exposures from Guilarte *et al.* (2006).

Studies that used sc injection for Mn delivery typically used much higher Mn doses (Table 1) to overcome the poor bioavailability and absorption of the insoluble  $\text{MnO}_2$  form. Simulations of the two dose levels in Suzuki *et al.* (1975) and the single dose level in Eriksson *et al.* (1987) are shown in Figure 5. Globus pallidus Mn concentrations from the other sc studies (Eriksson *et al.*, 1992a,b; Pentschew *et al.*, 1963) displayed similar kinetic behavior, including a rapid rise in brain Mn concentrations immediately following injection followed by a slow decline to near basal levels that in some instances took over one year. Compared with ip and iv exposures, brain Mn concentrations from sc exposures remained elevated for much longer periods of time, which may be due to slow absorption of relatively insoluble Mn particles at the injection sites, as was reported by Eriksson *et al.* (1987). The model did underpredict globus pallidus concentration 1 year following the last sc exposure in Eriksson *et al.* (1987); however, because the focus of this analysis was on a comparison of brain Mn concentrations with clinical effects observed during the exposure period or shortly thereafter, parameters governing transfer from the sc compartment were selected to calibrate simulation results closer to the end of the exposure period. This underprediction could also be due to liver impairment following high-dose Mn exposure, which would reduce biliary excretion and lead to higher tissue Mn concentrations. This effect was not included in the model due to a lack of quantitative information regarding changes in hepatobiliary excretion rates following Mn exposure.

Inhalation exposure studies used several different forms of Mn ( $\text{MnO}_2$ ,  $\text{Mn}_3\text{O}_4$ , and  $\text{MnSO}_4$ ) of varying degrees of solubility (Bird *et al.*, 1984; Coulston and Griffin, 1976; Dorman *et al.*, 2006a; Nishiyama *et al.*, 1977). Model parameters were calibrated by Schroeter *et al.* (2011) to the time-course data from Dorman *et al.* (2006a) for a 90-day exposure to a  $\text{MnSO}_4$  atmosphere containing 1.5 mg Mn/ $\text{m}^3$  to simulate a rapid rise in brain Mn concentrations during the 90-day exposure followed by a return to near basal levels during the 90 days following cessation of exposure (Fig. 6). To account for differences in lung deposition and absorption due to the different particle densities, particle sizes, and solubilities of the Mn aerosols used in the other studies, a Deposition Adjustment Factor (DAF) was applied to the lung deposition fraction of Mn oxide particles to



**TABLE 2**  
**Severity Scores Applied to Clinical Effects Observed in Mn Exposure Studies in Monkeys**

| Study                             | Dose route | Monkey ID                          | Time until effect (days) | Observation  |                                     |                         |                      |                |                      | Sum |
|-----------------------------------|------------|------------------------------------|--------------------------|--------------|-------------------------------------|-------------------------|----------------------|----------------|----------------------|-----|
|                                   |            |                                    |                          | Coordination | Bradykinesia/<br>Gross motor skills | Rigidity/Gait disorders | Postural instability | Muscle tremors | Other clinical signs |     |
| Gupta <i>et al.</i> (1980)        | oral       | Group I                            | 540                      | 2            |                                     | 1                       |                      |                |                      | 3   |
| Van Bogaert and Dallemagne (1946) | oral       | 1                                  | 292                      |              |                                     |                         |                      |                |                      | 0   |
| Mella (1924)                      | ip         | 3                                  | 253                      | 2            |                                     |                         |                      |                | 1                    | 3   |
|                                   |            |                                    | 255                      | 2            |                                     | 1                       |                      |                | 1                    | 4   |
|                                   |            |                                    | 275                      | 2            |                                     | 1                       |                      | 1              |                      | 4   |
|                                   |            | 4                                  | 370                      | 2            |                                     |                         |                      |                | 1                    | 3   |
|                                   |            |                                    | 429                      | 2            |                                     | 1                       |                      |                | 1                    | 4   |
|                                   |            |                                    | 444                      | 2            |                                     | 2                       |                      | 1              |                      | 5   |
|                                   |            |                                    | 473                      | 2            |                                     | 3                       |                      | 2              | 2                    | 9   |
|                                   |            | 5                                  | 196                      | 1            |                                     | 1                       |                      |                | 1                    | 3   |
|                                   |            |                                    | 204                      | 1            |                                     | 1                       |                      |                | 2                    | 4   |
|                                   |            | 6                                  | 110                      | 1            |                                     |                         |                      |                |                      | 1   |
|                                   |            |                                    | 112                      | 1            |                                     |                         |                      |                | 1                    | 2   |
|                                   |            |                                    | 144                      | 1            |                                     |                         |                      |                | 2                    | 3   |
|                                   |            |                                    |                          |              |                                     |                         |                      |                |                      |     |
|                                   |            |                                    |                          |              |                                     |                         |                      |                |                      |     |
| Olanow <i>et al.</i> (1996)       | iv         | 1                                  | 10                       |              | 2                                   | 2                       | 1                    |                | 2                    | 7   |
|                                   |            | 2                                  | 12                       |              | 2                                   | 2                       | 1                    |                | 1                    | 6   |
|                                   |            | 3                                  | 49                       |              |                                     |                         |                      |                |                      | 0   |
| Guilarte <i>et al.</i> (2006)     | iv         | Group 1                            | 140                      | 1            |                                     |                         |                      |                |                      | 1   |
| Suzuki <i>et al.</i> (1975)       | sc         | 1                                  | 196                      | 1            | 1                                   |                         |                      |                |                      | 2   |
|                                   |            |                                    | 14                       |              |                                     |                         |                      | 1              |                      | 1   |
|                                   |            | 2                                  | 42                       |              | 2                                   |                         |                      | 1              |                      | 3   |
|                                   |            |                                    | 21                       |              |                                     |                         |                      | 1              |                      | 1   |
|                                   |            |                                    | 28                       | 2            |                                     |                         |                      | 1              | 1                    | 4   |
|                                   |            |                                    | 42                       | 2            |                                     | 2                       |                      | 1              | 2                    | 7   |
|                                   |            | 3                                  | 49                       |              |                                     |                         |                      |                | 1                    | 1   |
|                                   |            |                                    | 56                       | 2            |                                     | 2                       |                      |                | 2                    | 6   |
|                                   |            | 4                                  | 35                       | 2            |                                     |                         |                      |                | 1                    | 3   |
|                                   |            |                                    | 56                       | 2            |                                     | 2                       |                      |                | 2                    | 6   |
|                                   |            | 5                                  | 49                       |              |                                     |                         |                      | 1              |                      | 1   |
|                                   |            |                                    | 42                       |              |                                     |                         |                      | 1              |                      | 1   |
|                                   |            |                                    | 56                       |              |                                     |                         |                      | 1              | 1                    | 2   |
|                                   |            |                                    | 63                       | 2            |                                     | 2                       |                      |                | 2                    | 6   |
| Eriksson <i>et al.</i> (1987)     | sc         | 1                                  | 90                       | 1            |                                     | 1                       |                      |                | 1                    | 3   |
|                                   |            |                                    | 150                      | 1            | 2                                   | 2                       |                      |                |                      | 5   |
|                                   |            |                                    | 210                      | 1            | 2                                   | 2                       |                      | 1              | 1                    | 7   |
|                                   |            | 2                                  | 90                       | 1            | 2                                   | 2                       |                      | 2              |                      | 7   |
|                                   |            |                                    | 150                      | 2            | 2                                   | 2                       |                      | 2              |                      | 8   |
|                                   |            | 3 and 4                            | 150                      | 2            | 2                                   | 2                       |                      |                |                      | 6   |
| Eriksson <i>et al.</i> (1992a)    | sc         | 1                                  | 189                      |              |                                     |                         |                      |                |                      | 0   |
|                                   |            | 2                                  | 189                      |              | 1                                   |                         |                      |                |                      | 1   |
| Eriksson <i>et al.</i> (1992b)    | sc         | 1 and 2                            | 120                      | 1            | 2                                   | 2                       |                      |                |                      | 5   |
| Pentschew <i>et al.</i> (1963)    | im         | 1                                  | 270                      |              |                                     |                         | 2                    |                | 2                    | 4   |
|                                   |            |                                    | 435                      | 2            |                                     | 2                       | 2                    |                | 2                    | 8   |
| Bird <i>et al.</i> (1984)         | inhalation | Group 1                            | 730                      |              |                                     |                         |                      |                |                      | 0   |
| Nishiyama <i>et al.</i> (1977)    | inhalation | A                                  | 90                       | 1            | 1                                   |                         |                      | 1              |                      | 3   |
|                                   |            | B                                  | 300                      |              |                                     |                         |                      |                |                      | 0   |
| Coulston and Griffin (1976)       | inhalation | Low dose                           | 450                      |              |                                     |                         |                      |                |                      | 0   |
|                                   |            | High dose                          | 161                      |              |                                     |                         |                      |                |                      | 0   |
| Dorman <i>et al.</i> (2006)       | inhalation | Low, mid, and high exposure groups | 90                       |              |                                     |                         |                      |                |                      | 0   |

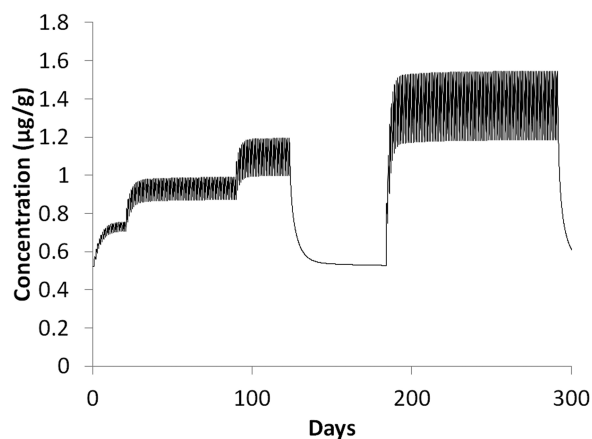


**FIG. 2.** PBPK model simulation of the globus pallidus Mn concentration with the dosing schedule from Van Bogaert and Dallemagne (1946). Oral Mn doses were given once daily: day 1–20: 1.3 mg/kg/day; day 21–89: 2.5 mg/kg/day; day 89–123: 3.8 mg/kg/day; day 124–183: 0 mg/kg/day; day 184–291: 6.3 mg/kg/day.

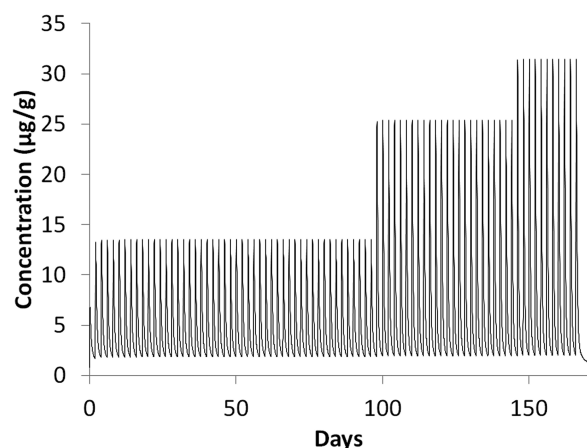


**FIG. 3.** Predicted Mn globus pallidus concentrations in monkey no. 6 from Mella (1924) subject to ip injection of Mn every other day. Dosing schedule: day 1–96: 0.9 mg/kg; day 97–144: 1.8 mg/kg; day 145–166: 2.2 mg/kg.

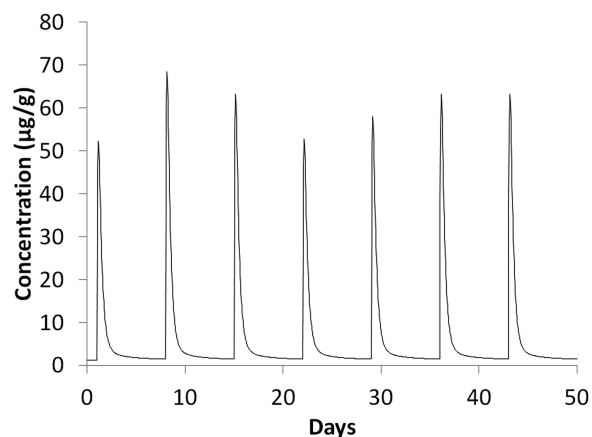


**FIG. 4.** Predicted Mn globus pallidus concentration in a monkey exposed by iv injection according to the dosing schedule from Olanow *et al.* (1996). The monkey was injected once a week with 2.8–3.6 mg/kg Mn.

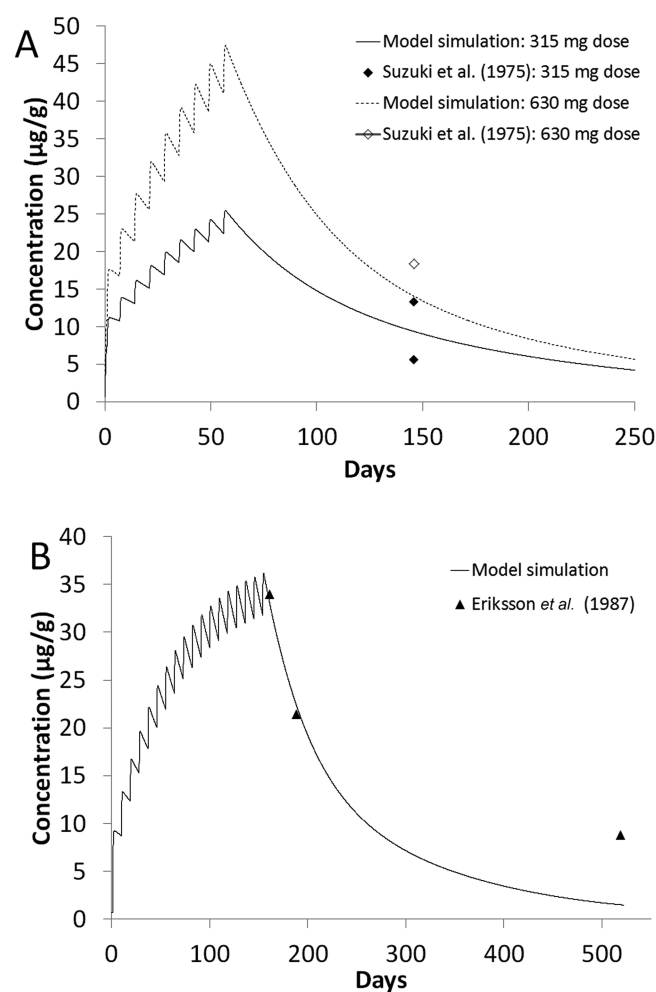


**FIG. 5.** Simulated globus pallidus concentrations in monkeys exposed by sc injection: (A) Monkeys were injected once a week for 9 weeks with 315 or 630 mg Mn/injection (Suzuki *et al.*, 1975); (B) Monkeys were injected on 18 occasions over 5 months with 444 mg Mn/injection (Eriksson *et al.*, 1987). The curves are model simulations, and the data points are measured globus pallidus concentrations from individual animals from Suzuki *et al.* (1975) and Eriksson *et al.* (1987).

account for their reduced bioavailability (Table 3). The DAF was calibrated based on measured end-of-exposure globus pallidus Mn concentrations. Simulations of the exposures from the Nishiyama *et al.* (1977) study are shown in Figure 6B. As with the Dorman simulations, brain Mn concentrations were predicted to rise during the exposure event and decrease once exposures stopped, although the predicted daily fluctuations from the Nishiyama simulations were less than those from the Dorman simulations due to the reduced bioavailability of the deposited Mn oxide particles in the lung. Even though the exposure concentration of 3.0 mg/m<sup>3</sup> was higher in the Nishiyama study, brain Mn concentrations were lower than in the Dorman study due to the lower solubility of MnO<sub>2</sub>. Model simulations of the Bird *et al.* (1984) and Coulston and Griffin (1976) studies showed similar behavior.

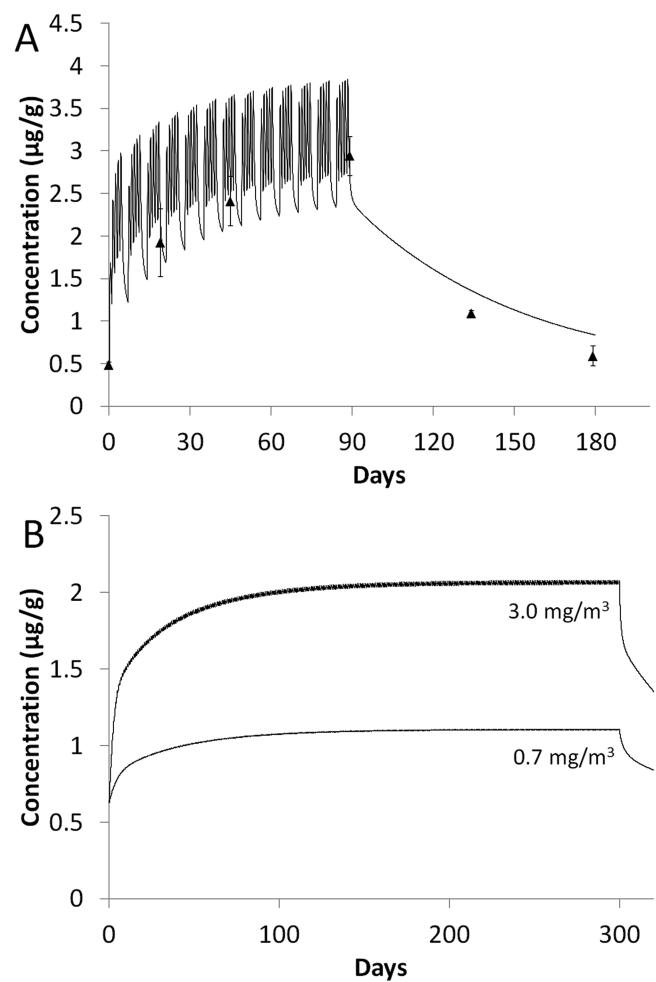


**FIG. 6.** Predicted globus pallidus concentrations in monkeys exposed by inhalation: (A) the exposure scenario from Dorman *et al.* (2006a): exposure to  $\text{MnSO}_4$  at 1.5 mg  $\text{Mn}/\text{m}^3$  for 6 h/day, 5 days/week for 90 days; (B) the exposure scenario from Nishiyama *et al.* (1977): exposure to  $\text{MnO}_2$  at 0.7 or 3.0 mg  $\text{Mn}/\text{m}^3$  for 22 h/day, 7 days/week for 10 months.

Dose-Response Analysis

The peak concentration, AUC (which represents cumulative internal dose), and average concentration for globus pallidus Mn concentrations during the exposure periods were computed from the PBPK model simulations for all of the dose groups from the Mn exposure studies included in this review. Severity scores applied to each dose group were plotted against all three dose metrics (Fig. 7). A steep dose-response behavior was observed when severity scores were plotted against peak globus pallidus Mn concentration (Fig. 7A). A visible pattern of increased severity was observed for peak concentrations greater than ~7 µg/g. When plotted against AUC, the progression of severity scores with exposure duration can be clearly observed (Fig. 7B). With the exception of a few dose groups (Nishiyama *et al.*, 1977; Olanow *et al.*, 1996), the severity scores started to increase for AUC values > 6000 (µg/g)-h. Although the dose-response behavior for all dose metrics exhibited significant scatter, the dose-response behavior for average concentration was not as evident, with increased severity scores for globus pallidus Mn concentrations between 4 and 30 µg/g (Fig. 7C).

A CatReg analysis was performed using the severity scores for the dose metrics of Mn peak concentration and AUC in the globus pallidus following Mn exposure. The dose metric of average globus pallidus Mn concentration was not considered for the regression analysis because the severity scores did not display a clear dose-dependent increase with concentration. Because the CatReg software limits severity scores to four categories, the severity scores summarized in Table 2 were combined to generate new severity scores for the regression analysis: 0:0, 1:1–3, 2:4–6, 3:7–9. These data were log transformed prior to the regression analysis. For the CatReg analysis, the *p* value was < 0.05 for both cases of peak concentration and AUC, indicating that the model fits were acceptable. *R*<sup>2</sup> values were 0.20 and 0.16 for the dose metrics of peak concentration and AUC, respectively, indicating that a small amount (20 and 16%) of

**TABLE 3**  
**Summary of Aerosol Parameters and Lung Deposition Factors Used for the Simulation of Mn Inhalation Exposures**

| Study                          | Mn form                        | Particle size            | Density (g/cm <sup>3</sup> ) | Exposure concentration (mg Mn/m <sup>3</sup> ) | Deposition adjustment factor | Reported increase in globus pallidus Mn concentration (%) | Predicted increase in globus pallidus Mn concentration (%) |
|--------------------------------|--------------------------------|--------------------------|------------------------------|------------------------------------------------|------------------------------|-----------------------------------------------------------|------------------------------------------------------------|
| Dorman <i>et al.</i> (2006a)   | MnSO <sub>4</sub>              | MMAD = 2.0 µm, GSD = 1.5 | 2.95                         | 1.5                                            | 1.0 <sup>a</sup>             | 513                                                       | 471                                                        |
| Bird <i>et al.</i> (1984)      | MnO <sub>2</sub>               | < 5 µm                   | 5.0                          | 30                                             | 0.0028 <sup>b</sup>          | 79                                                        | 80                                                         |
| Nishiyama <i>et al.</i> (1977) | MnO <sub>2</sub>               | < 2 µm                   | 5.0                          | 0.7                                            | 0.03 <sup>b</sup>            | 133 <sup>c</sup>                                          | 83                                                         |
| Coulston and Griffin (1976)    | Mn <sub>3</sub> O <sub>4</sub> | < 6 µm                   | 4.9                          | 3.0                                            | 0.4 <sup>b</sup>             | 183 <sup>c</sup>                                          | 250                                                        |
|                                |                                |                          |                              | 0.1                                            |                              | 122 <sup>c</sup>                                          | 107                                                        |
|                                |                                |                          |                              | 5.0                                            |                              | Not reported                                              | 990                                                        |

<sup>a</sup>The Dorman *et al.* (2006a) study was used to estimate model parameters, so there was no need to further adjust lung deposition.  
<sup>b</sup>Deposition adjustment factors were calibrated to reported globus pallidus Mn concentrations from the respective study.  
<sup>c</sup>Mn concentrations were reported in the basal ganglia. These values were used as surrogates for globus pallidus Mn concentrations.

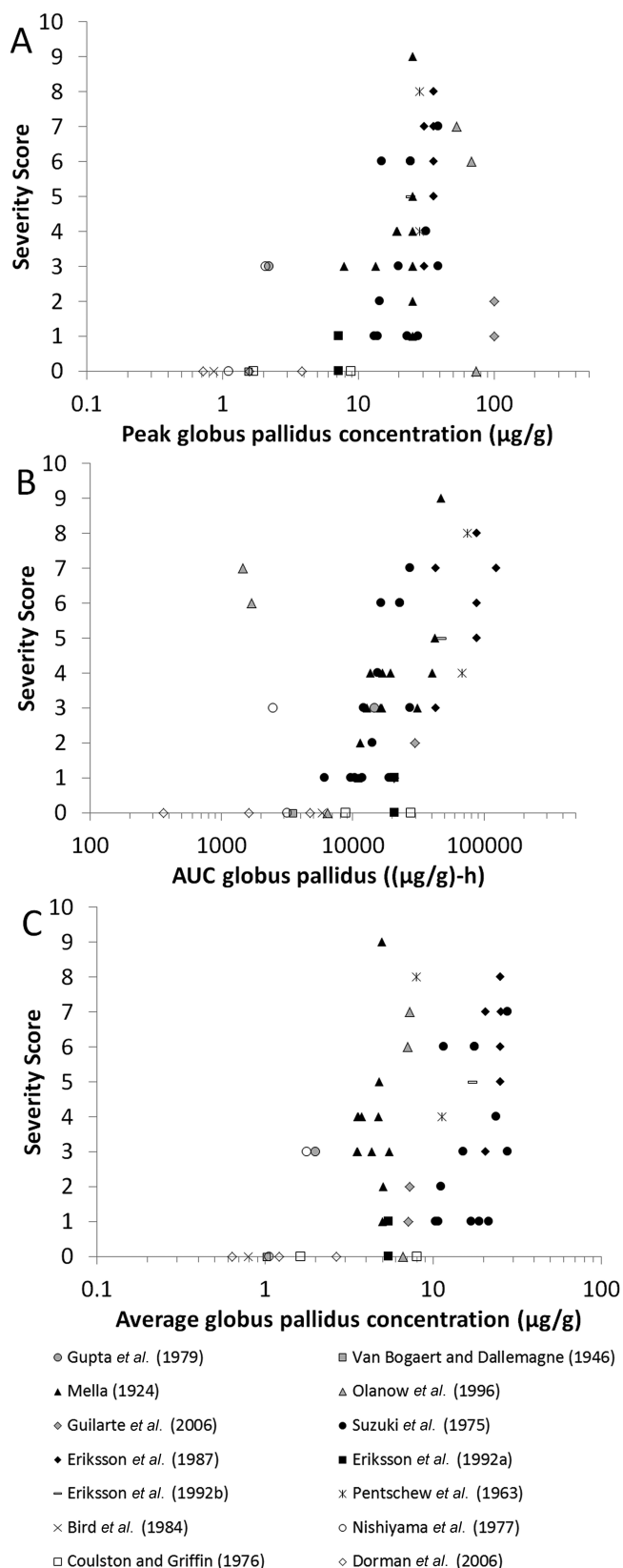


**FIG. 7.** Dose-response relationship for the Mn exposure studies using various dose metrics in the globus pallidus: (A) peak concentration, (B) area under the concentration curve (AUC), and (C) average concentration.

**TABLE 4**

**Results of the CatReg Analysis of Severity Scores for the Dose Metrics of Peak Concentration and AUC from the PBPK Model Simulations. ERD<sub>10</sub>, ERD<sub>20</sub>, and ERD<sub>30</sub> Correspond to 10, 20, and 30% Extra Risk, Respectively, of the Corresponding Severity Score**

| Severity score            | ERD <sub>10</sub> | ERD <sub>20</sub> | ERD <sub>30</sub> |
|---------------------------|-------------------|-------------------|-------------------|
| Peak concentration (µg/g) |                   |                   |                   |
| 1                         | 0.8               | 1.4               | 2.0               |
| 2                         | 5.5               | 9.6               | 13.9              |
| 3                         | 18.1              | 31.6              | 45.9              |
| AUC ((µg/g)-h)            |                   |                   |                   |
| 1                         | 813.1             | 1477.7            | 2198.2            |
| 2                         | 4860.7            | 8834.5            | 13141.7           |
| 3                         | 20283.9           | 36866.5           | 54840.2           |

the variability in the data was accounted for with the regression curve. The low  $R^2$  values are likely due to the fact that most studies reported incidence fractions of 0 or 1 because only one animal was typically used in each dose group.

CatReg was also used to provide a maximum likelihood estimate of the peak globus pallidus Mn concentrations and AUC values that would result in 10, 20, and 30% extra risk (denoted as ERD<sub>10</sub>, ERD<sub>20</sub>, and ERD<sub>30</sub>, respectively) of attaining severity grades 1, 2, and 3 (Table 4). For example, the estimated 10% extra risk of attaining a severity score of 1, as informed by the severity scores applied to each dose group, was achieved with a peak globus pallidus Mn concentration of 0.8 µg/g or an AUC value of 813.1 µg/g-h.

## DISCUSSION

An improved understanding of the dose-response relationships between Mn exposure, abnormally increased tissue Mn concentrations, and the development of neurotoxicity and other adverse clinical effects is a critical issue for Mn risk assessment. Many studies have been conducted to examine Mn-induced neurotoxicity in nonhuman primates. Most of these studies used elevated Mn doses, parenteral exposures, and variable dosing scenarios, making it difficult to extrapolate high-dose effects to potential responses from chronic low-dose inhalation exposure. There is also significant variability across studies regarding the onset and severity of neurotoxic effects. This variability is primarily due to the use of different forms of Mn and different exposure routes, leading to differences in Mn absorption, elimination, and tissue accumulation. Although it is difficult to extrapolate results from an individual study that may have only relied on several animals each acutely exposed to high Mn doses, a meta-analysis that utilizes a consistent measure of internal dose can reveal a clearer understanding of the dose-response behavior of Mn.

The analysis by Gwiazda *et al.* (2007) considered multiple studies on Mn neurotoxicity in Mn-exposed nonhuman

primates to see whether there was a consistent dose-response relationship. In their analysis, internal cumulative Mn dose was estimated from the nominal dose provided in the reviewed study (corrected for the weight fraction of Mn in the compound administered), the measured or estimated daily consumption of the exposure media, treatment duration, estimated fraction of Mn absorbed into the bloodstream, and the body weight of the animal. For the nonhuman primate studies, Gwiazda assumed Mn uptake rates of 3% for oral exposures and 100% for all other exposure routes. They reported that the cumulative Mn dose at which adverse effects were detected in monkeys was dependent on the chemical species of Mn administered. Adverse effects also demonstrated a dose dependency. For example, in monkeys, motor deficits and/or effects on the globus pallidus were seen at relatively low cumulative doses (between 20 and 70 mg Mn/kg). More profound effects and involvement of additional brain regions (e.g., caudate and putamen) were noted at higher cumulative exposure doses (> 260 mg Mn/kg). The range of exposures associated with adverse changes was over two orders of magnitude in the animal studies, which led Gwiazda *et al.* (2007) to conclude that most existing animal model studies might be of limited relevance for the risk assessment of chronic low-level Mn exposure to humans. Newland (1999) also reviewed the progressive effects of Mn exposure with increased dose from several studies, where dose was defined as the “cumulative dose of Mn in mg of Mn/kg body mass that had been administered when the sign appeared.” He concluded that there is considerable variability across studies in the latency to onset of neurotoxic effects associated with Mn.

Although these earlier reviews of Mn neurotoxicity estimated cumulative Mn dose, they did not take into account internal Mn kinetics, solubility differences among the sulfate, phosphate, and oxide forms of Mn used in different studies, dose-dependent biliary excretion, or increases in Mn concentrations within brain regions (e.g., the globus pallidus) that are target tissues for Mn neurotoxicity. In the present analysis, PBPK model simulations were used to estimate toxicologically relevant internal measures of Mn accumulation within the globus pallidus: peak concentration, average concentration, and cumulative internal dose (AUC) during the Mn exposure period. Rodent studies were not described in this evaluation because, unlike nonhuman primates, they lack behavioral similarities to humans and are less sensitive to Mn than are humans and nonhuman primates (Guilarte, 2010).

The PBPK model for Mn dosimetry was derived from a rich pharmacokinetic data set in rhesus monkeys exposed to Mn by inhalation (Dorman *et al.*, 2006a). Additional exposure routes in the model (oral, ip, iv, and sc) were validated using  $^{54}\text{Mn}$  clearance data, which showed differences in elimination rates depending on exposure route, but with all tracer studies displaying a biphasic elimination (Schroeter *et al.*, 2011). Because tracer studies reflect the overall kinetics of Mn in the body, this gives us significant confidence that the model captured the main dose-dependent characteristics of Mn uptake,

elimination, and distribution in monkeys. By accounting for dose-route differences in Mn absorption and elimination, we were able to estimate common dose metrics among the many Mn exposure studies that have been conducted in nonhuman primates, regardless of the exposure route, solubility, or dosing schedule used in the animal studies.

The PBPK model structure used in this study was originally developed to describe Mn tissue dosimetry in rats subject to dietary and inhalation exposure (Nong *et al.*, 2008). This model structure was subsequently extended to monkeys and humans with additional exposure routes added as needed to accommodate various experimental methods used to administer Mn and  $^{54}\text{Mn}$  (Nong *et al.*, 2009; Schroeter *et al.*, 2011). These modeling efforts helped inform key processes involved in Mn kinetics, including saturable tissue binding, asymmetric flux into brain regions, and dose-dependent biliary excretion that allow tissue Mn concentrations to remain fairly constant during low levels of exposure and to rise rapidly during high-dose episodes, as was observed in animals. The models have also been recently used to guide a tissue dose-based risk assessment approach and to study Mn tissue accumulation in sensitive subpopulations (Andersen *et al.*, 2010; Taylor *et al.*, 2012). The ability of the PBPK models to consistently describe Mn kinetics across multiple species and exposure routes indicates that the models have accurately captured the dose-dependent characteristics of Mn disposition. For this study, several parameters governing portal-of-entry effects were estimated to accurately simulate the delivery of Mn to the systemic circulation from multiple exposure routes. However, the parameters governing internal Mn kinetics, such as diffusion rate constants and tissue binding parameters, were unchanged for all simulations regardless of exposure route. Once further biochemical details for tissue binding, membrane transport, and Mn retention in enterocytes (to name a few examples) become available, then these parameters can be appropriately refined in the model. Slight reparameterization of other rate constants may then be necessary to maintain the same quality as the current model-fit with pharmacokinetic data in animals because, as pointed out by Schroeter *et al.* (2011), model simulations are sensitive to some parameters such as the biliary excretion and diffusion rate constants.

This analysis depended not only on an accurate estimation of tissue Mn concentrations following Mn exposure but also on a consistent application of severity scores to multiple studies from numerous investigators over a wide period of time. Our clinical understanding of neurochemical changes associated with Mn neurotoxicity has undergone significant revisions during the past decade as single photon emission computed tomography and positron emission tomography studies have been used. In addition, some studies performed in monkeys have assessed dopamine,  $\gamma$ -aminobutyric acid, and other neurotransmitters in Mn-exposed monkeys. Guilarte (2010) performed a thorough review of the available human and nonhuman primate Mn neurotoxicity data and concluded that there



is overwhelming evidence showing that Mn-induced neurological signs do not involve degeneration of midbrain dopamine neurons. Moreover, handling of brain tissue samples in some early neurochemistry studies (e.g., Neff *et al.*, 1969) was of concern because tissue samples from control and Mn-treated animals were subjected to different storage times and conditions (Guilarte, 2010). Thus, unlike Gwiazda *et al.* (2007), we did not focus on brain dopamine changes as an endpoint of interest in this re-evaluation because too few contemporary studies would support this analysis.

Clinical evaluations, including an assessment of animal behavior, are a key component in neurotoxicity testing (Tilson and Moser, 1992). One challenge associated with this study is the confidence we have in the ability of the original study investigators to assess clinical signs in Mn-exposed monkeys. The *a priori* use of a scoring system is known to improve the ability to detect subclinical disease in animals. Among the studies we reviewed, only the one performed by Guilarte *et al.* (2006) fully described their observational methods and provided a scoring scale. Guilarte rated a variety of behaviors using a scale developed for a monkey model of parkinsonism (Schneider and Kovelowski, 1990). Each item was rated as 0 (normal), 1 (mild), 2 (moderate), or 3 (severe) with disability (up to a maximum score) and dystonia/dyskinesia (maximum score of 21) being assessed individually. Guilarte also used an automated system to assess gross motor activity and a separate test apparatus to assess fine motor skills in their Mn-exposed animals. Guilarte *et al.* (2006) reported that behavioral rating scores in Mn-exposed monkeys increased slightly as the exposure duration progressed. Throughout the course of the study, animals appeared grossly normal and detected changes were considered very subtle (we rated these effects as mild with affected animals receiving a score of 2/17 in our scoring system).

Our data analysis is further complicated by the lack of detailed reporting of when clinical signs emerged (often given in weeks or months rather than days). For example, on the one hand, Mella (1924) provided a detailed account of clinical signs associated with Mn exposure every other day during the exposure period, whereas the study by Gupta *et al.* (1980) merely reported that clinical signs were evident after 18 months of exposure. In the latter case, because no other information was given regarding the onset of effects, we had to assume that they began at 18 months. Another confounder that should be recognized is that many of the studies fail to describe whether or not animal selection was randomized (unlikely given the extremely small numbers of animals used) or whether the person performing the animal observations were blinded to treatment groups. As in human studies, failure to control for these confounders often leads to an overestimate of the effect seen in animals (Bebarta *et al.*, 2003).

Our data analysis method also warrants examination. The clinical scoring system we used develops categorical data. The analysis of such categorical data has been less robustly explored in neurotoxicology (Markgraf *et al.*, 2010). We utilized a

descriptive approach that relied on the experience of the evaluator (David D. Dorman) to assess whether the reported clinical signs were abnormal and consistent with Mn neurotoxicity. Markgraf *et al.* (2010) compared the use of an experienced behavioral toxicologist to more routine statistical approaches in interpreting rodent functional observational battery data. Similar to our methods, the behavioral toxicologist evaluating the data sets in the Markgraf study was not blinded prior to evaluation. Markgraf found that professional judgments and statistical approaches yielded similar estimates of an individual study no-effect level.

Despite the use of different Mn forms, multiple exposure routes, a wide range of dose levels, and possible inconsistencies among studies regarding the reporting of Mn-induced effects, a clear dose-response behavior was observed when severity scores were analyzed versus the PBPK model-derived dose metrics of peak concentration and cumulative dose (AUC) in the globus pallidus region. This analysis can help inform threshold levels for dose-dependent transitions in effects from Mn exposure. The fact that peak concentration demonstrated a sharp transition in effects indicates the existence of a threshold brain Mn concentration for Mn-induced effects. For example, from the CatReg analysis, a 10% extra risk for a mild response (severity level 1) occurred at a peak concentration of 0.8 µg/g (Table 4). This value is 81% higher than the average basal Mn concentration in the globus pallidus from these studies. A rapid increase in severity score was observed for peak Mn concentrations > 7 µg/g. Likewise, when plotted against AUC, an increase in severity with cumulative dose was also observed, indicating a progression of effects with increasing dose and exposure duration.

Although most of the data points followed a sigmoidal dose-response curve, there were several exceptions, which were expected given the wide range of experimental conditions used in the studies. For example, for peak globus pallidus concentration (Fig. 7A), the results from the Gupta *et al.* (1980) study (oral dosing) and from the high-dose group (3.0 mg/m<sup>3</sup> inhalation exposure concentration) of the Nishiyama *et al.* (1977) study displayed mild clinical effects at lower peak brain concentrations (~2 µg/g). The Nishiyama study was the only inhalation exposure study in this analysis to observe Mn-induced clinical effects, despite other inhalation studies using higher exposure concentrations or having higher estimated brain Mn concentrations. Some possible reasons for these discrepancies are that brain Mn concentrations were reported by Nishiyama as µg Mn per g dry tissue weight in the basal ganglia region. To be consistent with model predictions, these values were reduced by 80% (Molokhia and Smith, 1967) to convert to wet weight. It is also possible that basal ganglia Mn concentrations are not a suitable surrogate for globus pallidus Mn concentrations, as the basal ganglia includes other brain regions in addition to the globus pallidus. The Gupta study observed mild effects after oral Mn dosing, whereas the study by Van Bogaert and Dallemagne (1946) did not report any effects after similar

oral dosing schedules. The peak concentration predicted for the Gupta study was slightly greater than that for the Van Bogaert and Dallemagne (1946) study, but when the data points were plotted versus AUC, both points fell in line with other studies, indicating the importance of accounting for exposure duration as a predictor of toxicity. These discrepancies may also be due to differences in Mn absorption among individuals or may reflect a dose-dependent transition region where some animals begin to show effects whereas others do not.

Another aberration in the dose-response curve for peak concentration occurred from one of the animals in the Olanow *et al.* (1996) study, where globus pallidus Mn concentrations were predicted to be almost 90  $\mu\text{g/g}$ , yet no clinical effects were observed. This contrasts with two other animals from the same study that received slightly lower Mn doses yet demonstrated severe clinical effects. Olanow attributed this to individual variability to Mn intoxication. Simulations of the Guilarte *et al.* (2006) study also predicted high brain Mn concentrations following iv injection of Mn, yet only mild effects were observed. Model predictions for high-dose Mn iv injections demonstrated rapid increases in tissue Mn concentrations immediately following the injection, followed by rapid decreases in the days following injection. This behavior led to lower AUC values compared with sc injections, where much slower decreases in tissue Mn concentrations were predicted. There was no data available to validate the rise in tissue Mn concentrations following iv injection. Model predictions could possibly be improved if data existed for brain Mn concentrations at several time points following iv injection. Although Guilarte *et al.* (2006) reported globus pallidus Mn concentrations in iv-injected monkeys, measurements were taken 33 days after the last Mn injection and therefore were of limited use for validating peak tissue concentrations that occur soon after injection.

Finally, we offer one additional comment regarding the interpretation of the dose-response data. Cumulative dose (AUC) correlated with toxicity at the high-exposure situations considered in this analysis. This conclusion does not imply that equivalent cumulative doses experienced over a much longer duration (e.g., 70 years) at lower daily doses would generate neurological effects. This current analysis clearly showed that the tissue concentration correlated with neurological responses. In the case of inhalation, the PBPK models demonstrate that at or below an identifiable dose-dependent transition point for tissue accumulation (exposures of approximately  $0.01 \text{ mg/m}^3$ ), tissue Mn does not increase significantly above background concentrations because of natural homeostatic mechanisms (Andersen *et al.*, 2010; Schroeter *et al.*, 2011). Our analysis, then, indicates that neurological responses in rhesus monkeys correlate well with integrated tissue exposure (i.e., AUC) above a limiting globus pallidus concentration of about  $7 \mu\text{g/g}$  (see Figure 7A).

An approach to risk assessment for inhaled Mn has been suggested that considers increases in target tissue dose above background tissue levels (Andersen *et al.*, 2010). The dose-response behavior presented here lends validity to this approach by

evaluating internal measures of dose in the central nervous system that relate to Mn toxicity. Homeostatic controls maintain relatively stable Mn tissue concentrations by regulating intestinal absorption and biliary excretion. Toxicity results when these homeostatic controls are overwhelmed under conditions of excessive exposure, which was common in many of the high-dose studies examined in this study. This analysis clearly demonstrates that the dose response for the neurotoxic effects of Mn is independent of exposure route and supports the use of peak or cumulative tissue Mn concentrations as appropriate dose metrics. This analysis also provides evidence of a dose-dependent transition in the mode of action for the neurological effects of Mn that should be considered in risk assessments for this essential metal.

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## REFERENCES

- Abboud, S., and Haile, D. J. (2000). A novel mammalian iron-regulated protein involved in intracellular iron metabolism. *J. Biol. Chem.* **275**, 19906–19912.
- Agency for Toxic Substances Disease Registry (ATSDR). (2000). *Toxicological Profile for Manganese*. U.S. Department for Health and Human Services, Public Health Service, Atlanta, GA.
- Alves, G., Thiebot, J., Tracqui, A., Delangre, T., Guedon, C., and Lerebours, E. (1997). Neurologic disorders due to brain manganese deposition in a jaundiced patient receiving long-term parenteral nutrition. *J. Parenter. Enteral Nutr.* **21**, 41–45.
- Andersen, M. E., Dorman, D. C., Clewell, H. J., 3rd, Taylor, M. D., and Nong, A. (2010). Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment. *J. Toxicol. Environ. Health Part A* **73**, 217–234.
- Aschner, M., Erikson, K. M., and Dorman, D. C. (2005). Manganese dosimetry: Species differences and implications for neurotoxicity. *Crit. Rev. Toxicol.* **35**, 1–32.
- Ballatori, N., Miles, E., and Clarkson, T. W. (1987). Homeostatic control of manganese excretion in the neonatal rat. *Am. J. Physiol.* **252**(5 Pt 2), R842–R847.
- Bebarta, V., Luyten, D., and Heard, K. (2003). Emergency medicine animal research: Does use of randomization and blinding affect the results? *Acad. Emerg. Med.* **10**, 684–687.
- Bird, E. D., Anton, A. H., and Bullock, B. (1984). The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey. *Neurotoxicology* **5**, 59–65.

- Bouchard, M. F., Sauvé, S., Barbeau, B., Legrand, M., Brodeur, M. È., Bouffard, T., Limoges, E., Bellinger, D. C., and Mergler, D. (2011). Intellectual impairment in school-age children exposed to manganese from drinking water. *Environ. Health Perspect.* **119**, 138–143.
- Chandra, S. V., Srivastava, R. S., and Shukla, G. S. (1979). Regional distribution of metals and biogenic amines in the brain of monkeys exposed to manganese. *Toxicol. Lett.* **4**, 189–192.
- Coulston, F., and Griffin, T. (1976). *Inhalation Toxicology of Airborne Particulate Manganese in Rhesus Monkeys*. EPA Contract 68-02-0710. Institute of Comparative and Human Toxicology, Albany Medical College, and New Mexico International Center of Environmental Safety, Holloman Air Force Base, New Mexico.
- Dastur, D. K., Manghani, D. K., and Raghavendran, K. V. (1971). Distribution and fate of <sup>54</sup>Mn in the monkey: Studies of different parts of the central nervous system and other organs. *J. Clin. Invest.* **50**, 9–20.
- Dorman, D. C., Struve, M. F., Marshall, M. W., Parkinson, C. U., James, R. A., and Wong, B. A. (2006a). Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. *Toxicol. Sci.* **92**, 201–210.
- Dorman, D. C., Struve, M. F., Wong, B. A., Dye, J. A., and Robertson, I. D. (2006b). Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. *Toxicol. Sci.* **92**, 219–227.
- Eriksson, H., Gillberg, P. G., Aquilonius, S. M., Hedström, K. G., and Heilbronn, E. (1992a). Receptor alterations in manganese intoxicated monkeys. *Arch. Toxicol.* **66**, 359–364.
- Eriksson, H., Tedroff, J., Thuomas, K. A., Aquilonius, S. M., Hartvig, P., Fasth, K. J., Bjurling, P., Långström, B., Hedström, K. G., and Heilbronn, E. (1992b). Manganese induced brain lesions in *Macaca fascicularis* as revealed by positron emission tomography and magnetic resonance imaging. *Arch. Toxicol.* **66**, 403–407.
- Eriksson, H., Mägisté, K., Plantin, L. O., Fonnum, F., Hedström, K. G., Theodorsson-Norheim, E., Kristensson, K., Ståhlberg, E., and Heilbronn, E. (1987). Effects of manganese oxide on monkeys as revealed by a combined neurochemical, histological and neurophysiological evaluation. *Arch. Toxicol.* **61**, 46–52.
- Fell, J. M., Reynolds, A. P., Meadows, N., Khan, K., Long, S. G., Quaghebeur, G., Taylor, W. J., and Milla, P. J. (1996). Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* **347**, 1218–1221.
- Furchner, J. E., Richmond, C. R., and Drake, G. A. (1966). Comparative metabolism of radionuclides in mammals. 3. Retention of manganese-54 in the mouse, rat, monkey and dog. *Health Phys.* **12**, 1415–1423.
- Goss, J. A., Barshes, N. R., Karpen, S. J., Gao, F. Q., and Wyllie, S. (2008). Liver ischemia and ischemia-reperfusion induces and traffics the multi-specific metal transporter Atp7b to bile duct canaliculi: Possible preferential transport of iron into bile. *Biol. Trace Elem. Res.* **122**, 26–41.
- Guilarte, T. R. (2010). Manganese and Parkinson's disease: A critical review and new findings. *Environ. Health Perspect.* **118**, 1071–1080.
- Guilarte, T. R., Chen, M. K., McGlothlin, J. L., Verina, T., Wong, D. F., Zhou, Y., Alexander, M., Rohde, C. A., Syversen, T., Decamp, E., et al. (2006). Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human primates. *Exp. Neurol.* **202**, 381–390.
- Gupta, S. K., Murthy, R. C., and Chandra, S. V. (1980). Neuromelanin in manganese-exposed primates. *Toxicol. Lett.* **6**, 17–20.
- Gwiazda, R., Lucchini, R., and Smith, D. (2007). Adequacy and consistency of animal studies to evaluate the neurotoxicity of chronic low-level manganese exposure in humans. *J. Toxicol. Environ. Health Part A* **70**, 594–605.
- Imbert, C., Bezard, E., Guitraud, S., Boraud, T., and Gross, C. E. (2000). Comparison of eight clinical rating scales used for the assessment of MPTP-induced parkinsonism in the Macaque monkey. *J. Neurosci. Methods* **96**, 71–76.
- Jiang, L., Ranganathan, P., Lu, Y., Kim, C., and Collins, J. F. (2011). Exploration of the copper-related compensatory response in the Belgrade rat model of genetic iron deficiency. *Am. J. Physiol. Gastrointest. Liver Physiol.* **301**, G877–G886.
- Kawamura, R., Ikuta, H., Fukuzumi, S., Yamada, R., Tsubaki, S., Kodama, T., and Kurata, S. (1941). Intoxication by manganese in well water. *Arch. Exp. Med.* **18**, 145–169.
- Kepler, G. M., Richardson, R. B., Morgan, K. T., and Kimbell, J. S. (1998). Computer simulation of inspiratory nasal airflow and inhaled gas uptake in a rhesus monkey. *Toxicol. Appl. Pharmacol.* **150**, 1–11.
- Klaassen, C. D. (1974). Biliary excretion of manganese in rats, rabbits, and dogs. *Toxicol. Appl. Pharmacol.* **29**, 458–468.
- Knapka, J. J., Barnard, D. E., Bayne, K. A. L., Lewis, S. M., Marriott, B. M., and Oftedal, O. T. (1995). Nutrition. In *Nonhuman Primates in Biomedical Research: Biology and Management* (B. T. Bennett, C. R. Abee, and R. Henrickson, Eds.), pp 211–248. Academic Press, New York, NY.
- Kondakis, X. G., Makris, N., Leotsinidis, M., Prinou, M., and Papapetropoulos, T. (1989). Possible health effects of high manganese concentration in drinking water. *Arch. Environ. Health* **44**, 175–178.
- Kurlan, R., Kim, M. H., and Gash, D. M. (1991). Oral levodopa dose-response study in MPTP-induced hemiparkinsonian monkeys: Assessment with a new rating scale for monkey parkinsonism. *Mov. Disord.* **6**, 111–118.
- Lucchini, R. G., Albini, E., Benedetti, L., Borghesi, S., Coccaglio, R., Malara, E. C., Parrinello, G., Garattini, S., Resola, S., and Alessio, L. (2007). High prevalence of Parkinsonian disorders associated to manganese exposure in the vicinities of ferroalloy industries. *Am. J. Ind. Med.* **50**, 788–800.
- Markgraf, C. G., Cirino, M., and Meredith, J. (2010). Comparison of methods for analysis of functional observation battery (FOB) data. *J. Pharmacol. Toxicol. Methods* **62**, 89–94.
- Mella, H. (1924). The experimental production of basal ganglion symptomatology in macacus rhesus. *Arch. Neurol. Psychiat.* **11**, 405–417.
- Molokhia, M. M., and Smith, H. (1967). Trace elements in the lung. *Arch. Environ. Health* **15**, 745–750.
- Myers, J. E., Thompson, M. L., Ramushu, S., Young, T., Jeebhay, M. F., London, L., Esswein, E., Renton, K., Spies, A., Boule, A., et al. (2003). The nervous system effects of occupational exposure on workers in a South African manganese smelter. *Neurotoxicology* **24**, 885–894.
- Neff, N. H., Barrett, R. E., and Costa, E. (1969). Selective depletion of caudate nucleus dopamine and serotonin during chronic manganese dioxide administration to squirrel monkeys. *Experientia* **25**, 1140–1141.
- Newland, M. C. (1999). Animal models of manganese's neurotoxicity. *Neurotoxicology* **20**, 415–432.
- Newland, M. C., and Weiss, B. (1992). Persistent effects of manganese on effortful responding and their relationship to manganese accumulation in the primate globus pallidus. *Toxicol. Appl. Pharmacol.* **113**, 87–97.
- Newland, M. C., Ceckler, T. L., Kordower, J. H., and Weiss, B. (1989). Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. *Exp. Neurol.* **106**, 251–258.
- Nishiyama, K., Suzuki, Y., Fujii, N., Yano, H., Ohnishi, K., and Miyai, T. (1977). Biochemical changes and manganese distribution in monkeys exposed to manganese dioxide dust. *Tokushima J. Exp. Med.* **24**, 137–145.
- Nong, A., Taylor, M. D., Clewell, H. J., 3rd, Dorman, D. C., and Andersen, M. E. (2009). Manganese tissue dosimetry in rats and monkeys: Accounting for dietary and inhaled Mn with physiologically based pharmacokinetic modeling. *Toxicol. Sci.* **108**, 22–34.
- Nong, A., Teeguarden, J. G., Clewell, H. J., 3rd, Dorman, D. C., and Andersen, M. E. (2008). Pharmacokinetic modeling of manganese in the rat IV: Assessing factors that contribute to brain accumulation during inhalation exposure. *J. Toxicol. Environ. Health Part A* **71**, 413–426.
- Olanow, C. W., Good, P. F., Shinotoh, H., Hewitt, K. A., Vingerhoets, F., Snow, B. J., Beal, M. F., Calne, D. B., and Perl, D. P. (1996). Manganese



- intoxication in the rhesus monkey: A clinical, imaging, pathologic, and biochemical study. *Neurology* **46**, 492–498.
- Pal, P. K., Samii, A., and Calne, D. B. (1999). Manganese neurotoxicity: A review of clinical features, imaging and pathology. *Neurotoxicology* **20**, 227–238.
- Pentschew, A., Ebner, F. F., and Kovatch, R. M. (1963). Experimental manganese encephalopathy in monkeys. A preliminary report. *J. Neuropathol. Exp. Neurol.* **22**, 488–499.
- Perl, D. P., and Olanow, C. W. (2007). The neuropathology of manganese-induced Parkinsonism. *J. Neuropathol. Exp. Neurol.* **66**, 675–682.
- Roels, H., Lauwerys, R., Buchet, J. P., Genet, P., Sarhan, M. J., Hanotiau, I., de Fays, M., Bernard, A., and Stanescu, D. (1987). Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system, and some biological indices. *Am. J. Ind. Med.* **11**, 307–327.
- Schneider, J. S., Decamp, E., Koser, A. J., Fritz, S., Gonczi, H., Syversen, T., and Guilarte, T. R. (2006). Effects of chronic manganese exposure on cognitive and motor functioning in non-human primates. *Brain Res.* **1118**, 222–231.
- Schneider, J. S., and Kovelowski, C. J., 2nd. (1990). Chronic exposure to low doses of MPTP. I. Cognitive deficits in motor asymptomatic monkeys. *Brain Res.* **519**, 122–128.
- Schroeter, J. D., Nong, A., Yoon, M., Taylor, M. D., Dorman, D. C., Andersen, M. E., and Clewell, H. J., 3rd. (2011). Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multi-route physiologically based pharmacokinetic models. *Toxicol. Sci.* **120**, 481–498.
- Suzuki, Y., Mouri, T., Suzuki, Y., Nishiyama, K., and Fujii, N. (1975). Study of subacute toxicity of manganese dioxide in monkeys. *Tokushima J. Exp. Med.* **22**, 5–10.
- Taylor, M. D., Clewell, H. J., 3rd, Andersen, M. E., Schroeter, J. D., Yoon, M., Keene, A. M., and Dorman, D. C. (2012). Update on a pharmacokinetic-centric alternative tier II program for MMT-part II: Physiologically based pharmacokinetic modeling and manganese risk assessment. *J. Toxicol.* Article ID 791431.
- Tilson, H. A., and Moser, V. C. (1992). Comparison of screening approaches. *Neurotoxicology* **13**, 1–13.
- Ulrich, C. E., Rinehart, W., Busey, W., and Dorato, M. A. (1979). Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. II. Clinical observations, hematology, clinical chemistry and histopathology. *Am. Ind. Hyg. Assoc. J.* **40**, 322–329.
- Van Bogaert, L., and Dallemagne, M. J. (1946). Approches experimentales des troubles nerveux du manganisme. *Monatsschrift. Psychiat. Neurol.* **111/112**, 61–89.
- Yoon, M., Schroeter, J. D., Nong, A., Taylor, M. D., Dorman, D. C., Andersen, M. E., and Clewell, H. J., 3rd. (2011). Physiologically based pharmacokinetic modeling of fetal and neonatal manganese exposure in humans: Describing manganese homeostasis during development. *Toxicol. Sci.* **122**, 297–316.



# A tissue dose-based comparative exposure assessment of manganese using physiologically based pharmacokinetic modeling—The importance of homeostatic control for an essential metal

P. Robinan Gentry<sup>a,\*</sup>, Cynthia Van Landingham<sup>a</sup>, William G. Fuller<sup>a</sup>, Sandra I. Sulsky<sup>b</sup>, Tracy B. Greene<sup>a</sup>, Harvey J. Clewell III<sup>c</sup>, Melvin E. Andersen<sup>c</sup>, Harry A. Roels<sup>d</sup>, Michael D. Taylor<sup>e</sup>, Athena M. Keene<sup>f</sup>

<sup>a</sup> Ramboll Environ US Corporation, 3701 Armand St., Monroe, LA 71201, United States

<sup>b</sup> Ramboll Environ US Corporation, Amherst, MA, United States

<sup>c</sup> ScitoVation, RTP, NC, United States

<sup>d</sup> Université Catholique de Louvain, Brussels, Belgium

<sup>e</sup> NIPERA, Durham, NC, United States

<sup>f</sup> Afton Chemical Corporation, Richmond, VA, United States

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## ABSTRACT

A physiologically-based pharmacokinetic (PBPK) model (Schroeter et al., 2011) was applied to simulate target tissue manganese (Mn) concentrations following occupational and environmental exposures. These estimates of target tissue Mn concentrations were compared to determine margins of safety (MOS) and to evaluate the biological relevance of applying safety factors to derive acceptable Mn air concentrations. Mn blood concentrations measured in occupational studies permitted verification of the human PBPK models, increasing confidence in the resulting estimates. Mn exposure was determined based on measured ambient air Mn concentrations and dietary data in Canada and the United States (US). Incorporating dietary and inhalation exposures into the models indicated that increases in target tissue concentrations above endogenous levels only begin to occur when humans are exposed to levels of Mn in ambient air (i.e.  $> 10 \mu\text{g}/\text{m}^3$ ) that are far higher than those currently measured in Canada or the US. A MOS greater than three orders of magnitude was observed, indicating that current Mn air concentrations are far below concentrations that would be required to produce the target tissue Mn concentrations associated with subclinical neurological effects. This application of PBPK modeling for an essential element clearly demonstrates that the conventional application of default factors to “convert” an occupational exposure to an equivalent continuous environmental exposure, followed by the application of safety factors, is not appropriate in the case of Mn. PBPK modeling demonstrates that the relationship between ambient Mn exposures and dose-to-target tissue is not linear due to normal tissue background levels and homeostatic controls.

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## 1. Introduction

Manganese (Mn) is an essential element required as a cofactor for many enzymes with key biological functions, yet studies demonstrate that adverse health effects occur following exposure to high concentrations. Manganese exposure can occur through the diet; releases from industrial sources such as ferroalloy production plants, iron and steel foundries, alkaline battery manufacture, power plants, and coke ovens; and other sources. Long-term exposures to high concentrations of Mn are neurotoxic, leading to deficits in neuromotor and cognitive domains (Guilarte, 2010, 2013; Roels et al., 2012).

Although risk assessments for Mn have attempted to quantitatively estimate potential toxicity from inhalation exposures including those in the ambient environment, many of these assessments rely largely on the results from occupational cohorts where exposures may be many orders of magnitude higher than ambient air exposures of the general population. Using external concentration as the “dose metric” may not adequately address nonlinearities in complex biological processes (e.g. absorption, metabolism), resulting in target tissue concentrations that are not linearly correlated with external concentrations. Accounting for these nonlinearities is especially important for chemicals that are essential elements, whereby individuals already have substantial background tissue levels resulting from typical dietary intake.

In evaluating target tissue dosimetry following chemical exposures, the application of physiologically-based pharmacokinetic (PBPK) models has been suggested as a valuable tool. These models provide a

\* Corresponding author.

E-mail address: [rgentry@ramboll.com](mailto:rgentry@ramboll.com) (P.R. Gentry).

method for integrating toxicological and pharmacokinetic data and provide valuable alternatives to using external exposures in risk assessment (Barton and Clewell, 2000; Clewell and Andersen, 1985; Clewell et al., 1995). Use of PBPK modeling is the preferred approach for estimating internal doses of chemical substances for route and species extrapolation, preferably at the target tissue, that would then be used in dose-response modeling for deriving acceptable regulatory levels (USEPA, 2005, 2006). PBPK models also offer advantages for extrapolation across large differences in exposure concentrations, such as those that exist when attempting to compare the potential for health effects at Mn concentrations from occupational studies to those following exposure to lower ambient air concentrations (Andersen et al., 1999). This investigation relies upon a published human PBPK model developed by Schroeter et al. (2011) to evaluate target tissue concentrations following reported occupational exposures, as well as measured ambient air concentrations of Mn and the potential for health effects.

Traditional approaches to risk assessment for noncancer toxicants use a threshold approach where safety factors are applied to the highest concentration of the toxic agent that does not elicit toxicity (the no observed adverse effect level [NOAEL] or a benchmark dose [BMD]) to estimate an acceptable exposure concentration where even sensitive subpopulations will be protected. Evaluating the “margin of safety” (MOS) is an alternative approach where the maximum amount of exposure producing no measurable adverse effect is divided by the actual amount of human exposure in a population to understand the magnitude of the difference between actual exposures and concentrations associated with potential for health effects. By examining the target tissue Mn concentrations associated with occupational air exposure concentrations for which adverse changes in one or more specific physiological functions have been reported, comparisons can be made to target tissue exposures expected following exposure to Mn from ambient air. The MOS thus reveals how much of an increase in the ambient Mn air concentrations would be required to produce target tissue levels at or near the range where adverse impacts might be expected to occur.

The approach applied in this assessment is grounded in the synthesis of all available data and information on biological mechanisms, examines the application of PBPK models in risk assessment, and provides a comparison to the traditional risk assessment approach that incorporates default adjustments. Our investigation demonstrates that use of a MOS approach for an essential nutrient such as Mn allows for a harmonized biologically-based approach to risk assessment that is more specific to the chemical of interest than the traditional approach that relies on safety factors. Toward this goal, we applied a human adult PBPK model for Mn (Schroeter et al., 2011) to investigate: 1) target tissue and corresponding air concentrations of Mn below which subclinical neurological effects would not be expected to occur, based on observations reported in workers in occupational studies; 2) target tissue concentrations corresponding to ambient air concentrations of Mn; and 3) the range of air concentrations associated with increases of Mn above background levels in the target tissue.

## 2. Materials and methods

Epidemiological, toxicological, and pharmacokinetic studies of Mn and exposure studies of the levels of Mn in the environment have been conducted, some of which have been reported in the published literature. However, all of these studies have been conducted independently of one another. The approach presented here allows for the integration of epidemiological, toxicological, and exposure data in a quantitative manner, along with pharmacokinetic data to lay the foundation for a new approach to dose-response and exposure analyses for Mn – the estimation of target tissue concentrations.

Epidemiological and toxicological studies that provided quantitative exposure and response data were selected. The epidemiological/toxicological/exposure data were evaluated to determine if the quantitative information could be used in combination with published PBPK models

to estimate target tissue concentrations of Mn and at what target tissue concentrations potential health effects would be expected. In addition, data sources from both Canada and the United States (US) were surveyed to provide data that would allow for the estimation of potential exposure to Mn in both the diet and ambient air. Potential exposure from ingestion of drinking water containing Mn was not considered.

### 2.1. Selection of epidemiological data

Literature involving occupational studies of workers exposed to Mn was identified through searches of PubMed and Google Scholar, as well as review of the citations/reference lists in the studies identified. The identified studies were reviewed to determine if sufficient quantitative information on Mn exposures were provided in order to allow modeling of tissue Mn concentrations in exposed workers. Ideally, the most useful epidemiological studies would include the following: 1) a well-defined exposed population with little or no exposure to other neurotoxicants, 2) a well-defined and appropriate comparison group, 3) objective measures of neurological deficits (e.g. as opposed to self-reported symptoms or measured effects of unknown clinical importance), 4) estimates of personal exposure to respirable fractions of Mn, and 5) neurological measures collected for the same individuals. At a minimum, studies needed to provide quantitative exposure estimates for respirable Mn and objective measures of neurological deficits. The level of detail necessary to model tissue concentrations of Mn requires individual exposure and response data; however, this is often absent from published studies. Therefore, the raw data was relied upon when available.

### 2.2. Exposure to manganese from ambient air<sup>1</sup>

Air monitoring data were obtained from publicly available databases in both Canada and the US for the years 1991 through 2014, inclusively, to allow estimation of potential Mn concentrations in the ambient air. Sources of air monitoring data were the Canadian National Air Pollution Surveillance Network (NAPS, 2015) and the US Technology Transfer Network Air Quality System (USEPA, 2015). Total suspended particles (TSP) and particulate matter (PM) with aerodynamic diameter less than or equal to 10  $\mu\text{m}$  ( $\text{PM}_{10}$ ), 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ), and between 10 and 2.5  $\mu\text{m}$  ( $\text{PM}_{10-2.5}$ ) were measured at these monitoring networks. The Canadian monitoring stations reported Mn concentrations from either  $\text{PM}_{2.5}$  or  $\text{PM}_{10-2.5}$ , while the US stations generally reported Mn concentrations from TSP,  $\text{PM}_{10}$ , and/or  $\text{PM}_{2.5}$ , with a small number also reporting  $\text{PM}_{10-2.5}$ . All available Mn measurements from 1991 to 2014 were used to estimate the mean concentration and 95% lower and upper confidence limits (95% CLs) of Mn in ambient air as presented in the Supplemental information. For the purpose of this study, respirable PM was defined as particulate matter  $\leq 10 \mu\text{m}$ . Estimates of mean concentrations of Mn from respirable particles were calculated as the sum of  $\text{PM}_{10}$  and  $\text{PM}_{10-2.5}$  for Canadian data, and  $\text{PM}_{10}$  for US data. In all cases, the estimated 95% CLs assumed a normal distribution of the data.

### 2.3. Exposure to manganese the diet<sup>2</sup>

Estimated daily dietary intake of Mn for Canadians was obtained from tables provided by Health Canada (2011). Values reported in microgram per kilogram ( $\mu\text{g}/\text{kg}$ ) body weight/day were converted to total daily intake using comparable body weight data for each age and gender category from US Department of Health and Human Service's 2009–2012 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2010, 2012). Estimated daily dietary intake of Mn for the US population was obtained from NHANES. Two sets of data (NHANES 2009–2010 and NHANES 2011–2012) were combined for

<sup>1</sup> See discussion presented in Supplemental information.

<sup>2</sup> See discussion presented in Supplemental information.

this analysis and the body weights were adjusted so that the combination provided a nationally representative sample of dietary intake (CDC, 2006, 2007). The amount of Mn in the food items consumed was determined using the United States Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies (FNNDS) (USDA, 2012), and the USDA National Nutrient Database for Standard Reference, SR27 (USDA, 2014). The FNNDS database provides the “recipes” which break down the food items in the NHANES database into the individual items in the SR27 database. The SR27 database provides the amount of Mn (in units of mg/100 g) for each food item in a recipe.

Using data from the three databases (NHANES, FNNDS, and SR27), estimates of the amount of Mn consumed daily in the diet were determined for specific age groups and gender combinations. Intake from both food and nutritional supplements was based on data from the NHANES dietary intake interview and the data on supplements provided by the CDC in NHANES 2009–2012.

#### 2.4. Application of the human PBPK Mn model

The development of the current human PBPK model for Mn compounds (Schroeter et al., 2011) builds upon previous models (Andersen et al., 2010; Leavens et al., 2007; Nong et al., 2008, 2009; Teeguarden et al., 2007a, 2007b, 2007c; Yoon et al., 2009a, 2009b, 2011). These models characterize the movement of Mn compounds in the body following intake by oral or inhalation routes, as well as target tissue concentrations of Mn in selected regions of the brain. The Schroeter et al. (2011) model also incorporates direct transport of Mn to the brain via the olfactory nerve (Leavens et al., 2007; Nong et al., 2008, 2009). They build upon integration of pharmacokinetic data for various Mn compounds in rats, monkeys, and humans (Dorman et al., 2012; Taylor et al., 2012), considering the significant physiological and biochemical differences between species (Schroeter et al., 2011).

The Schroeter et al. (2011) human PBPK model was the primary model used for this investigation. This PBPK model has the capability of simulating concurrent exposure to dietary and inhaled Mn. The structure for this model relies on the structure initially developed for the rat and the monkey (Nong et al., 2009). This structure was extended to humans to predict dietary and inhalation exposure conditions, with human tracer studies relied upon for verification. Information for the characterization of the kinetics of Mn in humans was based on  $^{54}\text{Mn}$  clearance studies in monkeys and humans (Dastur et al., 1971; Davidsson et al., 1988; Dorman et al., 2006a; Furchner et al., 1966; Mahoney and Small, 1968; Mena et al., 1967; Newland et al., 1987). Clearance behavior of Mn displayed biphasic kinetics, dose-dependent differences in elimination, and dependence on total Mn body burden, either from Mn in the diet or supplemental Mn exposures. The Schroeter et al. (2011) model has adequately simulated the results from  $^{54}\text{Mn}$  tracer kinetics from oral and inhalation exposures and also for multiple water-soluble Mn compounds (i.e. Mn sulfate [ $\text{MnSO}_4$ ], Mn (II) chloride [ $\text{MnCl}_2$ ]) administered by intraperitoneal, intravenous, or subcutaneous administration.

The results of the extensive modeling effort by Schroeter et al. (2011) identified that one of the primary species differences that affect Mn kinetics is dietary exposure. Because Mn is an essential nutrient, dose-dependent biological processes that regulate absorption, tissue storage, and elimination must be considered, with a focus on those external exposures that alter uptake processes in the gut. The current models (Nong et al., 2008, 2009; Schroeter et al., 2011, 2012; Yoon et al., 2009a, 2009b, 2011) have characterized these processes, specifically changes in intestinal absorption and biliary elimination, capturing the homeostatic controls that regulate Mn body burden.

In the Schroeter et al. (2011) model, estimation of the deposition of Mn particles in the lung was conducted using the Multiple-Path Particle Dosimetry Model (MPPD model) particle deposition software; (copyright Applied Research Associates Inc., Albuquerque, NM), which considered species-specific lung geometries, ventilatory rates and particle

properties. Data for  $\text{MnSO}_4$ , which is a more bioavailable compound than other forms of manganese (i.e. Mn dioxide [ $\text{MnO}_2$ ], Mn [III] phosphate), were relied upon for characterizing lung deposition, and hence, subsequent systemic distribution in the human model based on the available studies for characterizing lung deposition in the monkey (Aschner and Aschner, 2005; Bush et al., 1995; Dorman et al., 2006a, 2006b; Schroeter et al., 2008). The use of the sulfate form assumes the highest absorption and distribution of manganese in the tissues as other forms have lower absorption and are likely to result in lower tissue concentrations (Dorman et al., 2001; Vitarella et al., 2000).

Information regarding the particle size for the distribution of total dust particles of Mn measured in the occupational studies is necessary to incorporate into the MPPD model to estimate the deposition fractions that are used in the PBPK model. However, data on the mean or median particle diameter for the occupational Mn measurements were not provided in the published studies (Gibbs et al., 1999; Lucchini et al., 1999; Myers et al., 2003a; Roels et al., 1987a, 1987b, 1992). The most detailed information characterizing particle size distributions of total Mn in occupational settings were measured using personal air monitors. Therefore, these data were focused upon initially for simulations.

Information on the particle size distribution from measurements of Mn dust gathered at a large alkaline battery plant from 1987 to 1995 (Roels et al., 1992, 1999) was obtained from the author. This database represents approximately 1500 air sampling results (total and respirable dust), and demonstrates a bimodal distribution for the airborne Mn particles with one peak observed at 6.0–6.5  $\mu\text{m}$ , characteristic of respirable particles, and a second peak >8.5  $\mu\text{m}$ , characteristic of the non-respirable fraction. Because no additional information was available on the size distribution of the respirable concentration of Mn dust from any other occupational studies, the median particle diameter for respirable dust was assumed to be approximately 6  $\mu\text{m}$  in diameter. USEPA (1993) notes a similar median diameter cut point for the respirable dust fraction of 5  $\mu\text{m}$  based on information provided by Roels et al. (1992) and Roels (1993). Since information was not available regarding median particle size for the respirable and non-respirable fraction from other Mn-associated occupational cohorts, a Monte Carlo analysis using personal exposure measures from the one occupational cohort study with particle size distribution data available (Roels et al., 1999) was conducted to estimate a potential geometric standard deviation (GSD) that would encompass the respirable range of particles (defined as <10  $\mu\text{m}$ ), as well as each of the bimodal distribution peaks. These data (Roels et al., 1999) displayed a respirable particle size distribution with peaks at 5.0  $\mu\text{m}$  ( $d_{50}$ ) and 7.1  $\mu\text{m}$  ( $d_{100}$ ). This analysis predicts a median particle size of 6.0  $\mu\text{m}$  (GSD 3.4  $\mu\text{m}$ ). While this represents a large variation in the potential particle size distribution, a median particle diameter of 6  $\mu\text{m}$  (GSD 3.4  $\mu\text{m}$ ) for simulating occupational exposures was used in the MPPD model.

Additional simulations were conducted to evaluate the potential effect of the assumptions of particle diameter and GSD on the PBPK model estimates of target tissue concentration (e.g. Mn concentration in the globus pallidus) (Table 1). The model was allowed to simulate exposure concentrations ranging from 21 to 1317 micrograms per cubic meter ( $\mu\text{g}/\text{m}^3$ ) corresponding to the exposure range for respirable Mn dust in alkaline battery plant workers (Roels et al., 1992). The mass media aerosol diameter (MMAD) varied from 3 to 9  $\mu\text{m}$  with GSD values of 1.5  $\mu\text{m}$  or 3.4  $\mu\text{m}$ . At the lower concentrations of particles (<100  $\mu\text{g}/\text{m}^3$ ), relatively little change in target tissue concentration was predicted. At the highest concentration (1317  $\mu\text{g}/\text{m}^3$ ), the variation in target tissue concentration ranged from 7% less to 6% more than the value estimated using the MMAD of 6  $\mu\text{m}$  (GSD 3.4  $\mu\text{m}$ ) for simulating occupational exposures.

#### 2.5. Comparison with results from analyses in nonhuman primates

An analysis similar to that presented here was conducted by Schroeter et al. (2012) using manganese neurotoxicity studies



**Table 1**  
PBPK-predicted concentration in the globus pallidus ( $\mu\text{g Mn/g}$  of tissue) after occupational exposure (8 h/day, 5 days/week) for 1 year in a 77.7 kg man with a dietary intake of 3 mg Mn/day.

| $\mu\text{g Mn/m}^3$<br>respirable dust | MMAD = 3, GSD = 3.4,<br>head 54.2%, lungs 14.3% | MMAD = 6, GSD = 3.4,<br>head 69.8%, lungs 13.5% | MMAD = 9, GSD = 3.4,<br>head 78.8%, lungs 13.1% | MMAD = 3, GSD = 1.5,<br>head 54.9%, lungs 23.5% | MMAD = 6, GSD = 1.5,<br>head 81.3%, lungs 15.1% | MMAD = 9, GSD = 1.5,<br>head 91.3%, lungs 7.3% |
|-----------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| 0                                       | 0.39                                            |                                                 |                                                 |                                                 |                                                 |                                                |
| 21                                      | 0.45                                            | 0.46                                            | 0.46                                            | 0.45                                            | 0.46                                            | 0.47                                           |
| 46                                      | 0.50                                            | 0.52                                            | 0.52                                            | 0.51                                            | 0.53                                            | 0.53                                           |
| 65                                      | 0.53                                            | 0.55                                            | 0.56                                            | 0.55                                            | 0.57                                            | 0.57                                           |
| 104                                     | 0.59                                            | 0.61                                            | 0.63                                            | 0.61                                            | 0.63                                            | 0.63                                           |
| 163                                     | 0.65                                            | 0.68                                            | 0.70                                            | 0.68                                            | 0.71                                            | 0.70                                           |
| 179                                     | 0.67                                            | 0.70                                            | 0.71                                            | 0.70                                            | 0.72                                            | 0.72                                           |
| 201                                     | 0.69                                            | 0.72                                            | 0.73                                            | 0.72                                            | 0.74                                            | 0.74                                           |
| 243                                     | 0.72                                            | 0.75                                            | 0.77                                            | 0.75                                            | 0.78                                            | 0.78                                           |
| 244                                     | 0.72                                            | 0.75                                            | 0.77                                            | 0.75                                            | 0.78                                            | 0.78                                           |
| 265                                     | 0.74                                            | 0.77                                            | 0.79                                            | 0.77                                            | 0.80                                            | 0.80                                           |
| 314                                     | 0.77                                            | 0.80                                            | 0.82                                            | 0.80                                            | 0.83                                            | 0.83                                           |
| 319                                     | 0.77                                            | 0.81                                            | 0.83                                            | 0.81                                            | 0.84                                            | 0.84                                           |
| 468                                     | 0.85                                            | 0.89                                            | 0.92                                            | 0.89                                            | 0.93                                            | 0.93                                           |
| 499                                     | 0.87                                            | 0.91                                            | 0.93                                            | 0.91                                            | 0.95                                            | 0.95                                           |
| 530                                     | 0.88                                            | 0.93                                            | 0.95                                            | 0.93                                            | 0.97                                            | 0.96                                           |
| 613                                     | 0.92                                            | 0.97                                            | 0.99                                            | 0.97                                            | 1.01                                            | 1.01                                           |
| 634                                     | 0.93                                            | 0.98                                            | 1.00                                            | 0.98                                            | 1.02                                            | 1.02                                           |
| 796                                     | 0.99                                            | 1.05                                            | 1.08                                            | 1.05                                            | 1.10                                            | 1.10                                           |
| 907                                     | 1.04                                            | 1.10                                            | 1.14                                            | 1.10                                            | 1.16                                            | 1.15                                           |
| 1201                                    | 1.14                                            | 1.23                                            | 1.27                                            | 1.23                                            | 1.30                                            | 1.29                                           |
| 1317                                    | 1.19                                            | 1.27                                            | 1.33                                            | 1.28                                            | 1.36                                            | 1.35                                           |

MMAD: mass media aerosol diameter.

GSD: geometric standard deviation.

Head: percentage of Mn deposited in the head (nasal cavities and brain) as estimated by the MPPD model.

Lungs: percentage of Mn deposited in the lungs (tracheobronchial and pulmonary regions) as estimated by the MPPD model.

conducted in monkeys. Gwiazda et al. (2007) had conducted a review of subchronic to chronic rodent and nonhuman primate studies to determine whether a consistent dose-response relationship existed among different studies. The goal of the Gwiazda et al. (2007) review was to determine whether animal studies could be used to evaluate the neurotoxicity of chronic low-level manganese exposures in humans.

Since the completion of the Gwiazda et al. (2007) review and with the development of recent PBPK models (Nong et al., 2009; Schroeter et al., 2011; Yoon et al., 2011), it is now possible to estimate the target tissue concentrations that would be associated with exposures to manganese in rat or monkey studies. Schroeter et al. (2012) focused on applying PBPK modeling approaches to a subset of the monkey studies identified by Gwiazda et al. (2007). Unlike rats, monkeys develop regionally selective increases in brain manganese concentrations (Dorman et al., 2006a, 2006b; Newland et al., 1987, 1989; Eriksson et al., 1992; Aschner and Aschner, 2005) and behavioral effects similar to those reported for manganese affected humans (Olanow et al., 1996). Using a PBPK model for Rhesus monkeys, Schroeter et al. (2012) simulated exposure scenarios from each monkey study reported by Gwiazda et al. (2007) and predicted the corresponding concentrations in the brain for various dose routes, exposure concentrations and durations. The observed responses were categorized using a clinical scoring system for dose-response analysis. We also compared results from this earlier analysis in monkeys to the current analyses relying on occupational studies.

## 2.6. Statistical analysis approach

A no-statistical-significance-of-trend (NOSTASOT) approach was used to estimate the NOAEL in target tissue (Tukey et al., 1985), using the data that indicated whether each individual had an adverse neurological test response combined with the PBPK model estimated Mn target tissue concentrations. The data separated into two groups (exposed lowest to highest by the PBPK model predicted concentration of Mn in the globus pallidus. A Fisher's exact test was used to compare the combined incidence rate of abnormal scores for eye-hand coordination or

the hand steadiness test between the exposed and unexposed groups. If there was a significant difference in incidence of an abnormal score between the exposed and unexposed group, the test was repeated after removing the subject(s) from the exposed group with the highest concentration of Mn in the globus pallidus. This process continued until a Fisher's exact test comparing the prevalence rate of abnormal neurological test response in the remaining exposed group to the prevalence rate in the unexposed group was not statistically significant. Removing the highest exposed individuals until a point was reached of no statistical significance allowed for the identification of a target tissue concentration NOAEL.

A second approach using the Tukey et al. (1985) NOSTASOT to derive a NOAEL used the Cochran-Armitage trend test (Armitage, 1955; Cochran, 1954). As with the method described above using the Fisher's exact test, this approach involves repeated application of a test for a significant dose-response trend grouping only by the PBPK model predicted concentration of Mn in the globus pallidus. If there is a significant difference in the complete data set, the test is repeated after removing the highest dose group. This procedure is repeated until the trend test is no longer statistically significant.

## 3. Results

### 3.1. Relevant epidemiological data

Twenty-one occupational studies with Mn exposure were initially identified (Bast-Pettersen et al., 2004; Bouchard et al., 2007a, 2007b; Deschamps et al., 2001; Fittro et al., 1992; Gibbs et al., 1999; Health Canada, 2010; Lee et al., 2003; Lees-Haley et al., 2006; Lucchini et al., 1995, 1997, 1999; Mergler et al., 1994; Myers et al., 2003a, 2003b, 2003c; Roels et al., 1987a, 1987b, 1992, 1999; Young et al., 2005). Emphasis was placed on occupational studies because these studies have provided the basis for current regulatory recommendations regarding inhalation exposure to Mn compounds (USEPA, 1998). Fourteen were selected for detailed review (Bast-Pettersen et al., 2004; Bouchard et al., 2007a, 2007b; Deschamps et al., 2001; Gibbs et al., 1999; Lucchini et al., 1999; Mergler et al., 1994; Myers et al., 2003a, 2003b, 2003c;

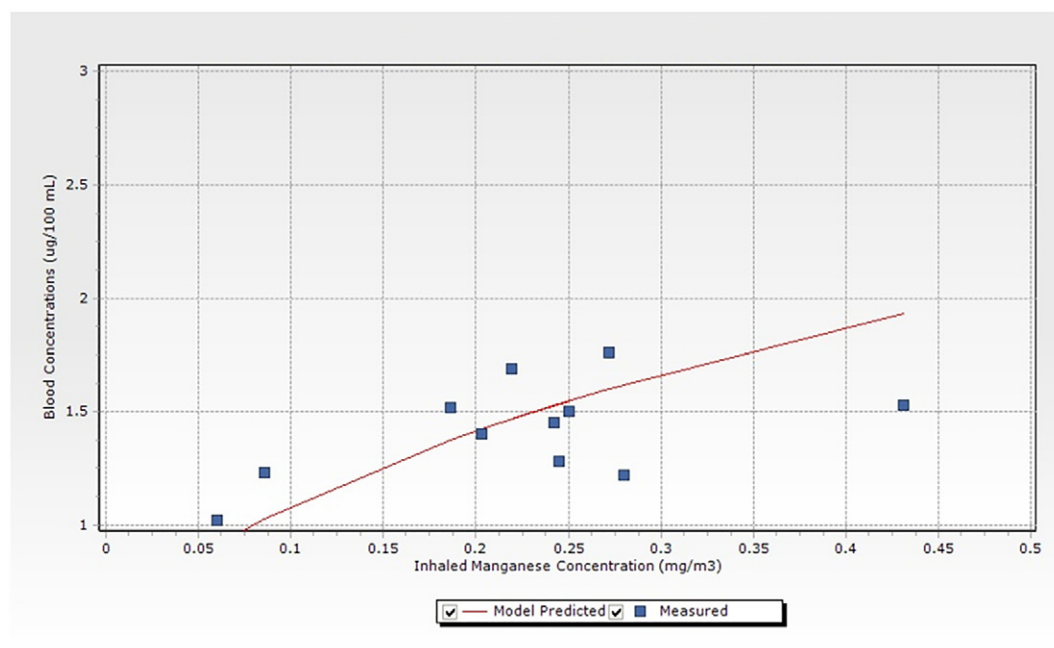


Fig. 1. Data from Roels et al. (1987a)—respirable Mn vs. blood concentrations at start of work week.

Roels et al., 1987a, 1987b, 1992, 1999; Young et al., 2005) that reported having the data necessary for quantitative exposure estimates and objective measures of neurological effects. Full individual exposure and response data were available for three of these studies (Bast-Pettersen et al., 2004; Roels et al., 1992, 1999<sup>3</sup>) and partial exposure and response data were available in seven studies (Bouchard et al., 2007a, 2007b; Gibbs et al., 1999<sup>3</sup>; Mergler et al., 1994; Myers et al., 2003a, 2003b; Young et al., 2005). Published studies provided data that were used in verifying the PBPK model and/or estimating Mn target tissue levels (Lucchini et al., 1999; Myers et al., 2003a; Roels et al., 1987a).

### 3.2. Exposure to manganese from ambient air and the diet

The estimated background air mean Mn concentrations and 95% confidence limits (CLs) for each country and respirable PM size (<10  $\mu\text{m}$ ) are 0.013  $\mu\text{g}/\text{m}^3$  (CL 0.012–0.013  $\mu\text{g}/\text{m}^3$ ) in Canada and 0.014  $\mu\text{g}/\text{m}^3$  (CL 0.013–0.016  $\mu\text{g}/\text{m}^3$ ) in the US (see Supplemental information). The estimated respirable ambient air concentration of Mn used in our PBPK models ranged from 0.01–0.02  $\mu\text{g}/\text{m}^3$ .

For occupational exposure modeling, the dietary exposure was 3 mg Mn per day based on average dietary intakes of Mn for Canadian and US populations (see Supplemental information). This value could be an underestimate of the mean dietary intake of adults in both the US and Canada as values of Mn from the dietary data reported in NHANES ranged up to >20 mg/day from diet alone (CDC, 2012) and to values >60 mg/day when supplements were also considered (Supplemental Table S4).

### 3.3. Verification of the human PBPK Mn model

The Mn PBPK models were developed using tissue and whole body concentration data, but due to their physiological structure, the models also can predict blood concentrations. To demonstrate that the simulated Mn blood concentrations from our PBPK model were consistent with those measured in occupational studies, available blood concentrations (Roels et al., 1987a) were compared to blood Mn concentrations simulated with the adult human PBPK model (Schroeter et al., 2011). Since

specific information on particle size distribution for this cohort was not available, the median particle size and GSD from a later study (Roels et al., 1992) were applied and exposure was simulated for 8 h/day, 5 days/week. As occupational exposure is not continuous and “steady state” would not be achieved, the model was run until the pattern of blood concentrations observed reached a constant, recurrent pattern, referred to as “periodicity”. Estimates of the blood concentration at the beginning and end of the work week were determined for comparison to the published data (Roels et al., 1987a).

The results of the PBPK modeling were similar in trends with the available Mn blood concentrations (Roels et al., 1987a), whether it was assumed that the blood samples were drawn from the workers at the beginning or the end of the work week (Figs. 1, 2). The model was applied without incorporation of available information on variability of physiological parameters, and thus does not reflect individual variability observed from individual blood measurements. However, the model simulation is consistent with the available measured Mn blood concentrations, particularly for individuals with lower exposures, a point that is critical for the evaluation of ambient exposures.

The PBPK model-predicted results from another study (Myers et al., 2003c) are shown along with the measured blood data (Figs. 3, 4). The simulations were compared with the blood draws at either the start or the end of the work week.

The data from a study measuring Mn blood concentrations in a group of ferroalloy workers (Lucchini et al., 1999) was also considered for comparison with the PBPK model. However, there were both internal (Lucchini et al., 1999) and external (Health Canada, 2010) inconsistencies related to estimating the fraction of inhaled Mn in the respirable range. In the publication (Lucchini et al., 1999), the authors reported that the respiratory fraction of Mn (as  $\text{MnO}_2$  and  $\text{Mn}_3\text{O}_4$ ) ranged from 40 to 60%. However, comparison of the values reported in the publication for total Mn dust (5–1490  $\mu\text{g}/\text{m}^3$ ; geometric mean 54.25  $\mu\text{g}/\text{m}^3$ ; arithmetic mean 175.59  $\mu\text{g}/\text{m}^3$ ) to respirable dust (1–670  $\mu\text{g}/\text{m}^3$ ; geometric mean 17.18  $\mu\text{g}/\text{m}^3$ ; arithmetic mean 67.08  $\mu\text{g}/\text{m}^3$ ) suggests a lower respirable fraction, 20–40%. Examination of individual data by Health Canada (2010), presenting the range, median, and mean concentrations across all job categories for total and respirable dust, suggests that only a limited number of “intermittent” samples of respirable Mn were taken. Health Canada (2010) relied upon these data to estimate the average respirable concentrations (ARE) over the duration of the

<sup>3</sup> Roels et al. (1992, 1999) and Gibbs et al. (1999) data were supplemented by raw data from authors.

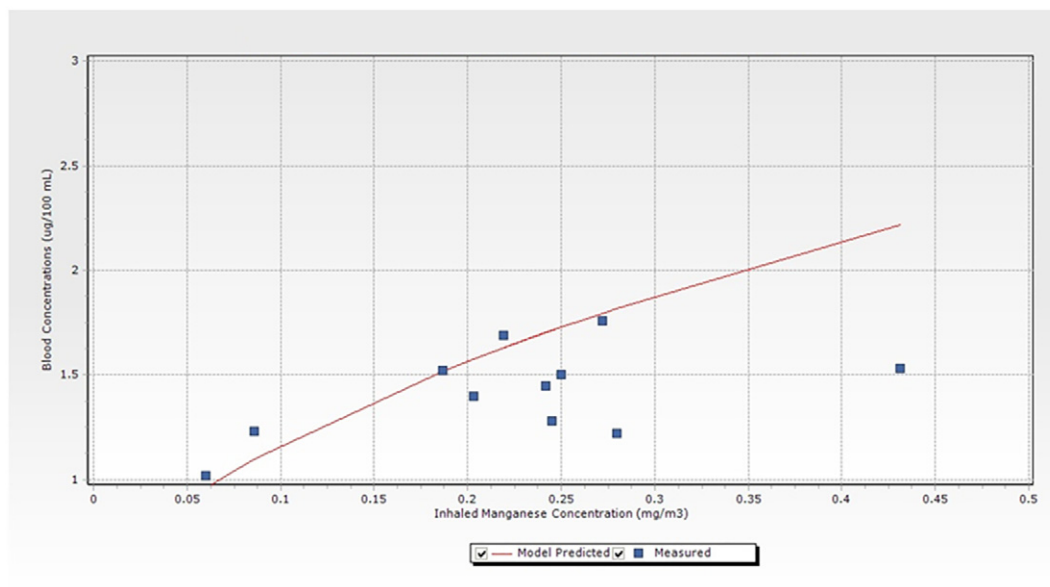


Fig. 2. Data from Roels et al. (1987a)—respirable Mn vs. blood concentrations at end of work week.

work history for each subject and over a shorter 5 year period (ARE5). Comparing the Health Canada (2010) estimates of ARE (1.21 to 285.16  $\mu\text{g}/\text{m}^3$ , arithmetic mean of 70.92) or ARE5 (1.1 to 145.43  $\mu\text{g}/\text{m}^3$ , arithmetic mean of 41.79) to the total dust concentrations reported by Lucchini et al. (1999) suggested that the respirable fraction of Mn could range from approximately 10–25% of the total concentration.

The estimates of the respirable fraction of Mn have a significant effect on predicted Mn blood concentrations from the Lucchini et al. (1999) study (Fig. 5). Using 20–60% as the respirable fraction gives a better match for expected blood Mn concentrations associated with total Mn dust concentrations of  $<0.2 \text{ mg}/\text{m}^3$ . For total Mn dust concentrations  $>0.2 \text{ mg}/\text{m}^3$ , however, model results are more consistent with a 20% respirable fraction. This outcome illustrates how different

assumptions made for the respirable fraction affects model results for Mn in target tissue. Thus, the use of dose metrics from this study (Lucchini et al., 1999) for the evaluation of Mn target tissue concentrations associated with potential adverse effects carries a high degree of uncertainty.

Since a strong agreement between model estimates and measured blood Mn concentrations is found in two of the three available occupational studies that report blood concentrations (Myers et al., 2003a; Roels et al., 1987a), the confidence in the model using data from these studies is higher. While the data necessary to validate the target tissue concentration of concern (i.e. increases of Mn in selected regions of the brain) are not available, the ability to simulate the available Mn blood concentrations measured in workers, as well as the available

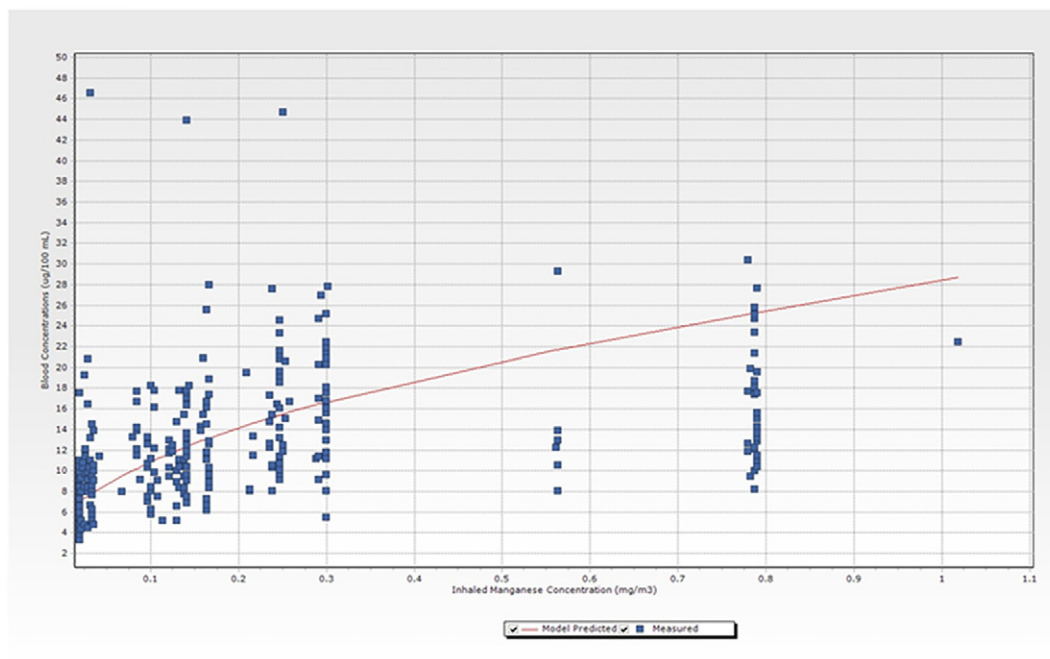


Fig. 3. Data from Myers et al. (2003a)—respirable Mn vs. modeled blood concentration at start of work week.

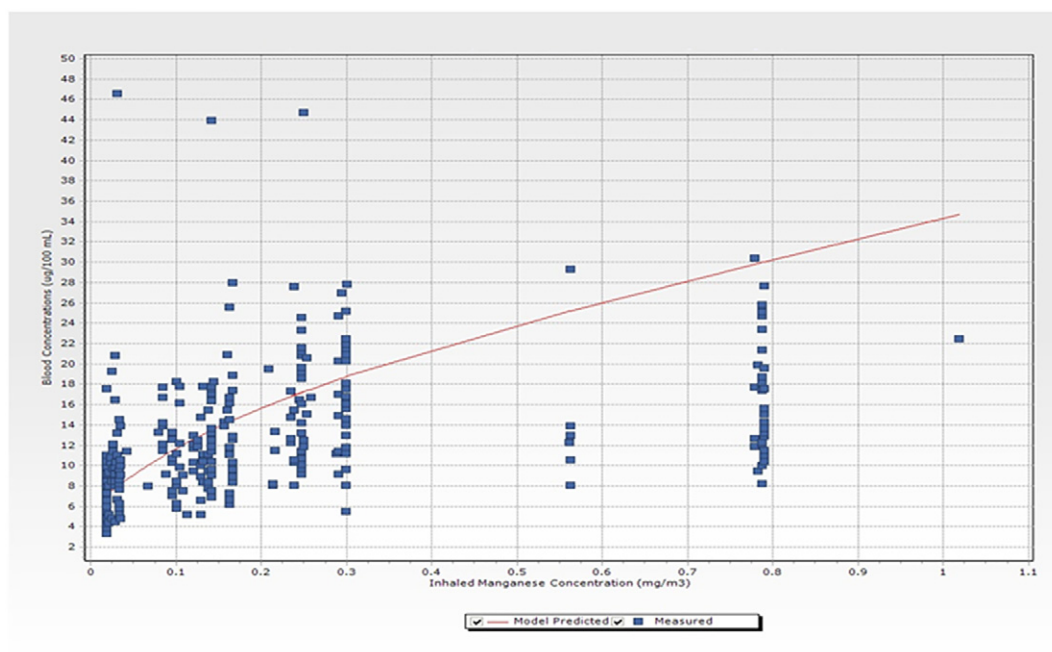


Fig. 4. Data from Myers et al. (2003a)—respirable Mn vs. modeled blood concentrations at end of work week.

data from human tracer studies, provides additional confidence in the estimates provided by the PBPK model. Further confidence comes from the ability of the primate model to accurately predict target tissue concentrations over an even greater range of dose-routes, including intravenous, intraperitoneal, and subcutaneous, in addition to inhalation and oral (Schroeter et al., 2012).

#### 3.4. Application of the human PBPK Mn model

Based on the changes in specific, subclinical neurological effects associated with Mn air concentrations reported in several occupational studies, the increase of Mn in the globus pallidus of the brain can be viewed as the relevant target tissue for neurological effects (Guilarte, 2010; Health Canada, 2010). Thus, the PBPK model can be used to derive

a “target tissue NOAEL” by applying the model to simulate the concentration of Mn expected in the globus pallidus following exposures at the highest air concentrations reported to have no effect on neurological function.

Exposure information and individual dichotomized data (response/no response) were available for each subject in a study of workers exposed to Mn oxide dust in a dry alkaline battery factory (Roels et al., 1992). This study evaluated the prevalence of neuropsychological symptoms and neurofunctional performance, thus allowing several types of analyses to be conducted to estimate a potential Mn target tissue NOAEL. The PBPK model was applied using data from this study (Roels et al., 1992), simulating the available respirable air concentrations for each individual and assuming 8 h/day, 5 day/week inhalation exposure. The target tissue concentrations (i.e. µg Mn/g tissue in the

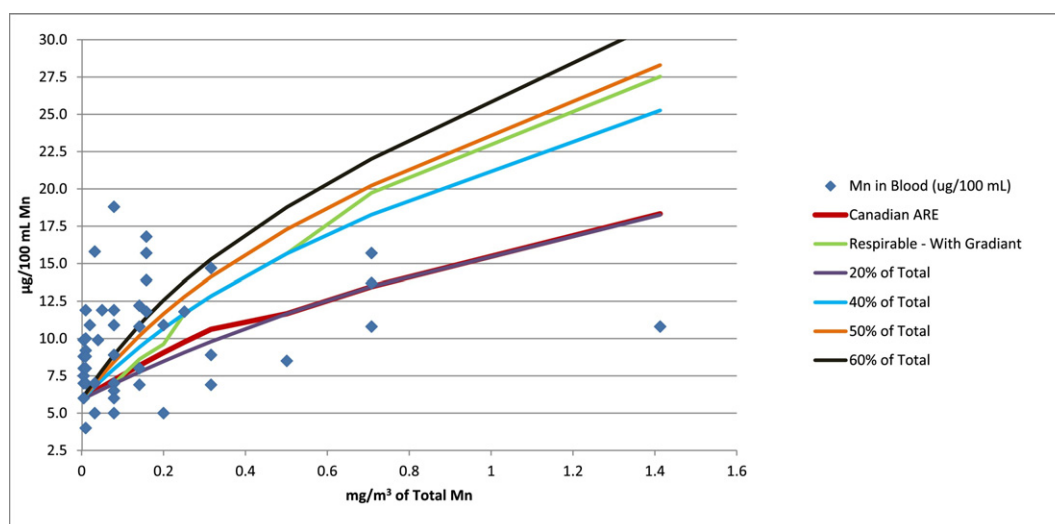


Fig. 5. Data from Lucchini et al. (1999)—impact of respirable fraction of Mn on blood concentration estimates.



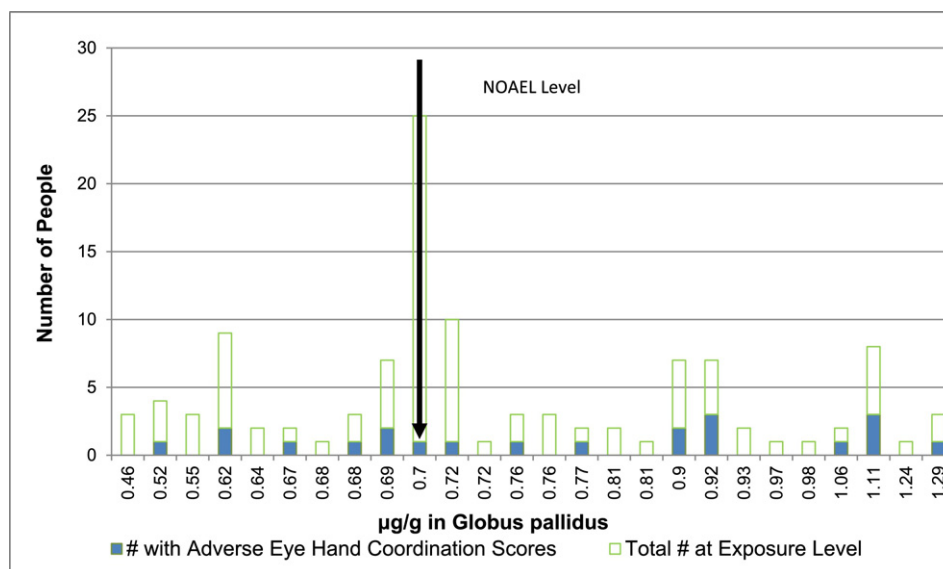


Fig. 6. Data from Roels et al. (1992)—individuals with adverse eye-hand coordination scores vs. globus pallidus Mn concentrations at end of work week.

globus pallidus) were estimated for each individual and used to determine a potential Mn target tissue NOAEL.

No-statistical-significance-of-trend (NOSTASOT) approach with a Fisher's exact test predicts a target tissue (Mn concentration in the globus pallidus) NOAEL of 0.7 µg/g using the prevalence rate of abnormal eye-hand coordination, (Fig. 6) and a target tissue NOAEL of 0.9 µg/g using the adverse effect endpoint of abnormal hand steadiness (Fig. 7). Applying the NOSTASOT statistical approach using trend tests to the data from the Roels et al. (1992) study, using eye-hand coordination data grouped into the same seven exposure groups (Table 2) determined by ATSDR (2012), yields a NOAEL corresponding to the exposure group with respirable continuous Mn concentrations of 100–199 µg/m<sup>3</sup> consistent with the ATSDR (2012) BMDL of 142 µg/m<sup>3</sup>, with a corresponding PBPK modeled target Mn tissue concentration of 0.7 µg/g. These two different statistical evaluations provided similar results.

Other epidemiological studies identified through literature searching reported no statistically significant abnormal neurofunctional test results following Mn exposure in occupational cohorts, even in the

highest exposure groups (Myers et al., 2003a; Gibbs et al., 1999). One study (Myers et al., 2003a) evaluated nervous system effects in a large cohort of South African mineworkers exposed to concentrations of Mn in the workplace. Only total dust Mn concentrations were reported, so it was assumed that the respirable fraction of the total dust Mn also changed as the concentration increased. The range of total dust Mn (digitized from Fig. 3 of Myers et al., 2003a) was 58 µg/m<sup>3</sup>–5088 µg/m<sup>3</sup>. Due to the shallow rise in the blood levels associated with the rise in the total dust, it appeared that the percentage of respirable dust declined with increasing total dust. Three different fractions were assumed for converting the total dust to respirable dust. For values of 58–<500 µg/m<sup>3</sup> of total dust, the assumed percentage of respirable dust was 33%. For values of 500–<1000 µg/m<sup>3</sup> of total dust, the assumed percentage of respirable dust was 25% and for concentrations of total Mn dust of ≥1000 µg/m<sup>3</sup>, the respirable fraction was assumed to be 20% of the total dust. These assumptions result in a range of respirable concentrations of Mn dust of 19–1018 µg/m<sup>3</sup>. Since this study did not report any neurological effects associated with any

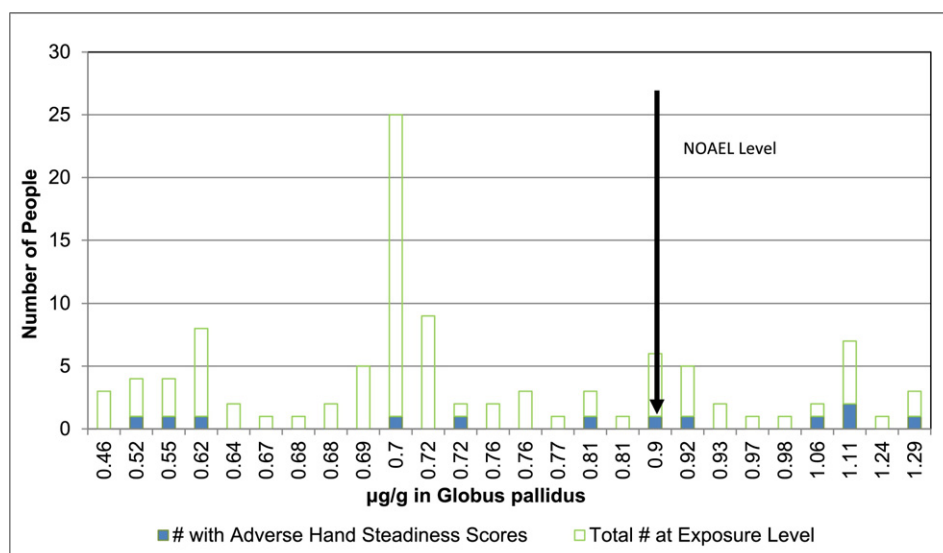


Fig. 7. Data from Roels et al. (1992)—individuals with adverse hand steadiness scores vs. globus pallidus concentrations of Mn at end of work week.

**Table 2**

Grouped prevalence data for abnormal eye-hand coordination scores in workers exposed to respirable manganese.

| Group    | Range of respirable manganese exposure concentrations ( $\mu\text{g Mn}/\text{m}^3$ ) | Average respirable manganese exposure concentrations ( $\mu\text{g Mn}/\text{m}^3$ ) | # of workers with abnormal eye-hand coordination scores | Total number of workers in exposure group |
|----------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------|
| 1        | Control                                                                               | 0                                                                                    | 5                                                       | 101                                       |
| 2        | 1.0–99                                                                                | 33                                                                                   | 1                                                       | 7                                         |
| <b>3</b> | <b>100–199</b>                                                                        | <b>174</b>                                                                           | <b>6</b>                                                | <b>39</b>                                 |
| 4        | 200–299                                                                               | 224                                                                                  | 4                                                       | 28                                        |
| 5        | 300–399                                                                               | 307                                                                                  | 2                                                       | 3                                         |
| 6        | 400–499                                                                               | 451                                                                                  | 4                                                       | 9                                         |
| 7        | >500 (523–650)                                                                        | 564                                                                                  | 4                                                       | 6                                         |

Source: ATSDR, 2012, based on Roels et al., 1992. The BMDL<sub>10</sub> used in the MRL derivation is  $142 \mu\text{g}/\text{m}^3$  (ATSDR, 2012).

Bolded data are those corresponding to the NOAEL.

exposure groups, the highest respirable concentration could be considered a NOAEL. Based on these assumptions, the PBPK model was run resulting in estimates of approximately  $1 \mu\text{g}/\text{g}$  tissue in the globus pallidus, which could be considered the NOAEL. Similarly, a study in which a population of US workers exposed to low levels of Mn dust were evaluated for subclinical neurological effects (Gibbs et al., 1999) reported no significant effects on neurofunctional performance at monthly average respirable Mn air concentrations as high as  $328 \mu\text{g}/\text{m}^3$ . Therefore, the highest air concentration reported for this study could be considered a NOAEL and the PBPK model, assuming an occupational exposure scenario (8 h/day, 5 days/week), provides an estimate of a Mn target tissue NOAEL of approximately  $0.8 \mu\text{g}/\text{g}$ .

In conducting the PBPK modeling simulations of the occupational exposures, it was assumed that there was no significant contribution to internal dose resulting from the ingestion of non-respirable particulates.

### 3.5. Comparison with results from analyses in nonhuman primates

The results from the Schroeter et al. (2012) analysis suggested a clear dose-response behavior of effects versus peak and cumulative dose area under the curve (AUC) in the globus pallidus region of the brain. Using a CatReg analysis, a 10% extra risk for a mild response, which would be comparable to subclinical effects such as those measured in human occupational studies, occurred at a peak concentration of  $0.8 \mu\text{g}/\text{g}$  manganese in the globus pallidus estimated using the PBPK model. This is consistent with the target tissue NOAELs  $0.7 \mu\text{g}/\text{g}$  Mn (eye-hand coordination) to  $0.9 \mu\text{g}/\text{g}$  Mn (hand steadiness scores) estimated in the current analysis.

### 3.6. Estimation of target tissue levels based on ambient air monitoring

Evaluation of the available air monitoring data from both Canada and the US (see Supplemental information) indicate that the 95% upper confidence limit (UCL) on the mean ambient respirable Mn air concentrations are approximately  $0.01$ – $0.02 \mu\text{g}/\text{m}^3$ . The concentration of Mn in the globus pallidus associated with this ambient air concentration was estimated using the median diameter of Mn-containing particles based on the relationship between the amount of Mn measured in filters with a  $2.5 \mu\text{m}$  cut-point and a cut-point between  $2.5$  and  $10 \mu\text{m}$ . Values of  $1.5$  and  $2.5 \mu\text{m}$  were used for the median particle size diameters with a standard deviation of  $1.5$ .

The PBPK model was applied assuming continuous exposure concentrations of  $0.01$ – $0.02 \mu\text{g}/\text{m}^3$  for 10 years to ensure that the target tissue concentrations achieved steady state. The modeling results indicated that this was achieved within 100 days for dietary exposure alone. The model estimated a target tissue concentration of Mn of  $0.4 \mu\text{g}/\text{g}$  with only dietary exposure. For occupational exposure, comparable patterns of tissue concentration (considering that occupational exposure is not continuous) were achieved within 200 days. In addition, in order to determine the ambient air concentrations that would be

needed to result in target tissue concentrations similar to those reported for the target tissue NOAEL from occupational studies, the PBPK model was applied assuming continuous exposure, increasing the concentration of respirable Mn until a target tissue concentration of approximately  $1 \mu\text{g}/\text{g}$  globus pallidus was achieved (Table 3, Fig. 8). This would be an exposure to respirable dust of at least  $150 \mu\text{g}/\text{m}^3$ .

### 3.7. Estimation of margins of safety based on target tissue concentrations

To develop a MOS, the continuous ambient air concentration associated with target tissue NOAELs from Roels et al. (1992) ( $0.7 \mu\text{g}/\text{g}$  Mn for eye-hand coordination;  $0.9 \mu\text{g}/\text{g}$  Mn for hand steadiness scores) was compared to the 95% UCL on the mean on the ambient air concentration ( $0.01$  to  $0.02 \mu\text{g}/\text{m}^3$ ). Based on the results of PBPK modeling, continuous exposure to an ambient air concentration of  $50 \mu\text{g}/\text{m}^3$  would be associated with a target tissue concentration of approximately  $0.7 \mu\text{g}/\text{g}$  Mn (Table 3), while continuous exposure to an ambient air concentration of  $120 \mu\text{g}/\text{m}^3$  would be associated with a target tissue concentration of approximately  $0.9 \mu\text{g}/\text{g}$  Mn. Based on these results, the MOS would be approximately 2500–5000 (calculated as  $50 \mu\text{g}/\text{m}^3$  divided by  $0.02 \mu\text{g}/\text{m}^3$  or  $0.01 \mu\text{g}/\text{m}^3$ ). For the target NOAEL based on results from neuropsychological testing to measure hand steadiness, the MOS would be approximately 6000–12,000 (calculated as  $120 \mu\text{g}/\text{m}^3$  divided by  $0.02 \mu\text{g}/\text{m}^3$  or  $0.01 \mu\text{g}/\text{m}^3$ ).

In all of the current regulatory assessments, application of adjustment factors have been applied to “convert” an occupational air concentration to an ambient air concentration and then safety factors have been applied. These approaches implicitly assume that any effect is linearly related to the external air concentration. However, the results of this analysis demonstrate that target tissue concentrations are not linearly associated with external air concentrations due to homeostatic

**Table 3**

Ambient respirable Mn concentrations vs. PBPK estimates of Mn concentration in globus pallidus.

| $\mu\text{g}/\text{m}^3$ respirable dust | Total $\mu\text{g}/\text{g}$ in globus pallidus |
|------------------------------------------|-------------------------------------------------|
| 0.01                                     | 0.39                                            |
| 0.1                                      | 0.39                                            |
| 1                                        | 0.41                                            |
| 10                                       | 0.50                                            |
| 20                                       | 0.57                                            |
| 30                                       | 0.63                                            |
| 40                                       | 0.67                                            |
| 50                                       | 0.71                                            |
| 60                                       | 0.74                                            |
| 70                                       | 0.77                                            |
| 80                                       | 0.80                                            |
| 90                                       | 0.83                                            |
| 100                                      | 0.85                                            |
| 110                                      | 0.87                                            |
| 120                                      | 0.89                                            |
| 130                                      | 0.91                                            |
| 140                                      | 0.93                                            |
| 150                                      | 0.95                                            |

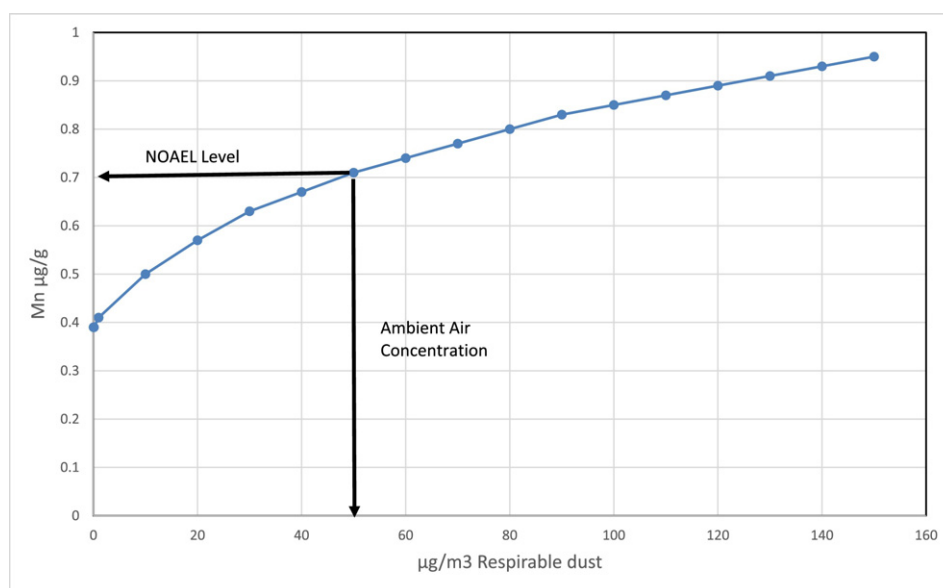


Fig. 8. Predicted total Mn ( $\mu\text{g/g}$ ) in the globus pallidus from exposure to varying amounts of respirable Mn dust.

mechanisms that maintain target tissue levels within a certain range of exposure. With the application of the PBPK model, Table 4 demonstrates that decreasing an ambient air concentration by safety factors of 10 does not result in corresponding decreases in the target tissue concentrations.

#### 4. Discussion

Current regulatory assessments for Mn rely on occupational studies to provide a point of departure (POD), which would be adjusted by safety factors to derive an acceptable Mn ambient air concentration. However, an approach that relies on the application of safety factors is only biologically reasonable if reductions in acceptable air Mn concentrations are associated with reductions in the concentration of Mn in target tissues. Incorporating PBPK modeling into the safety assessment for Mn allows consideration of available quantitative data, rather than applying default uncertainty or safety factors for this essential element.

Application of the PBPK model to estimate Mn concentrations in target tissues following occupational inhalation exposure demonstrated that there will not necessarily be linear decreases in target tissue Mn with decreasing Mn air concentrations. When the external Mn air concentration is below the concentration that would result in an increase in target tissue concentrations above background Mn, these air concentrations would not be associated with health effects. Decreases in concentrations assumed with the use of additional safety factors would not result in lower target tissue Mn concentrations (Table 4).

One uncertainty noted for the current analysis is the potential contribution from ingestion of Mn resulting from the non-respirable fraction of Mn in the occupational studies. The current analysis only incorporates the contribution from inhalation of respirable particles. The concentrations and particle sizes reported for the available occupational studies suggest there could be non-respirable Mn inhaled and removed from the respiratory tract via mucociliary processes and then swallowed, resulting in the potential for swallowed particles to contribute to target tissue concentrations. Inclusion of this additional contribution to estimated target tissue concentrations would result in an increase in the target tissue concentration associated with the NOAEL, so would only increase the MOS. Using information from Roels et al. (1992), inhalation exposure of workers to 1 Mn mg/m<sup>3</sup> total dust (80% is non-respirable) would result in approximately 8 mg Mn available for potential transfer to the gastrointestinal tract (assuming 10 m<sup>3</sup> of air inhaled for an 8 h workday). PBPK model-predicted concentrations in the globus pallidus following exposure to various dietary levels (Fig. 9a) indicate that the contribution due to swallowing the non-respirable fraction of inhaled particles could increase the target tissue concentration by approximately a factor of 2. The contribution from diet of 8 mg/day only results in approximately 0.65  $\mu\text{g/g}$  Mn in striatum/globus pallidus which, if considered, could potentially increase the NOAEL from 0.7  $\mu\text{g/g}$  Mn to approximately 1.4  $\mu\text{g/g}$  Mn or a factor of 2.

In addition, while the current study does not directly assess potentially sensitive subpopulations (e.g. susceptibility in fetal or neonatal children), Yoon et al. (2011) developed a PBPK model to integrate the available information on Mn kinetics during gestation and lactation in

Table 4

Target tissue concentrations of Mn associated with Mn ambient air concentrations derived from applying adjustment factors to NOAEL values.

| Study                | NOAEL concentration of Mn in the target tissue, globus pallidus ( $\mu\text{g/g}$ ) | Ambient air concentration ( $\mu\text{g Mn/m}^3$ ) | After applying adjustment factors of:           |                                                     |                                                 |                                                     |                                                 |                                                     |
|----------------------|-------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------|-----------------------------------------------------|-------------------------------------------------|-----------------------------------------------------|-------------------------------------------------|-----------------------------------------------------|
|                      |                                                                                     |                                                    | 10                                              |                                                     | 100                                             |                                                     | 1000                                            |                                                     |
|                      |                                                                                     |                                                    | Ambient air concentration ( $\mu\text{g/m}^3$ ) | Mn conc. in the globus pallidus ( $\mu\text{g/g}$ ) | Ambient air concentration ( $\mu\text{g/m}^3$ ) | Mn conc. in the globus pallidus ( $\mu\text{g/g}$ ) | Ambient air concentration ( $\mu\text{g/m}^3$ ) | Mn conc. in the globus pallidus ( $\mu\text{g/g}$ ) |
| Roels et al. (1992)  | 0.7                                                                                 | 47                                                 | 4.7                                             | 0.5                                                 | 0.47                                            | 0.4                                                 | 0.047                                           | 0.4                                                 |
|                      | 0.9                                                                                 | 124                                                | 12.4                                            | 0.5                                                 | 1.24                                            | 0.4                                                 | 0.124                                           | 0.4                                                 |
| Myers et al. (2003a) | 1                                                                                   | 157                                                | 15.7                                            | 0.6                                                 | 1.57                                            | 0.4                                                 | 0.157                                           | 0.4                                                 |
| Gibbs et al. (1999)  | 0.8                                                                                 | 80                                                 | 8                                               | 0.5                                                 | 0.8                                             | 0.4                                                 | 0.08                                            | 0.4                                                 |

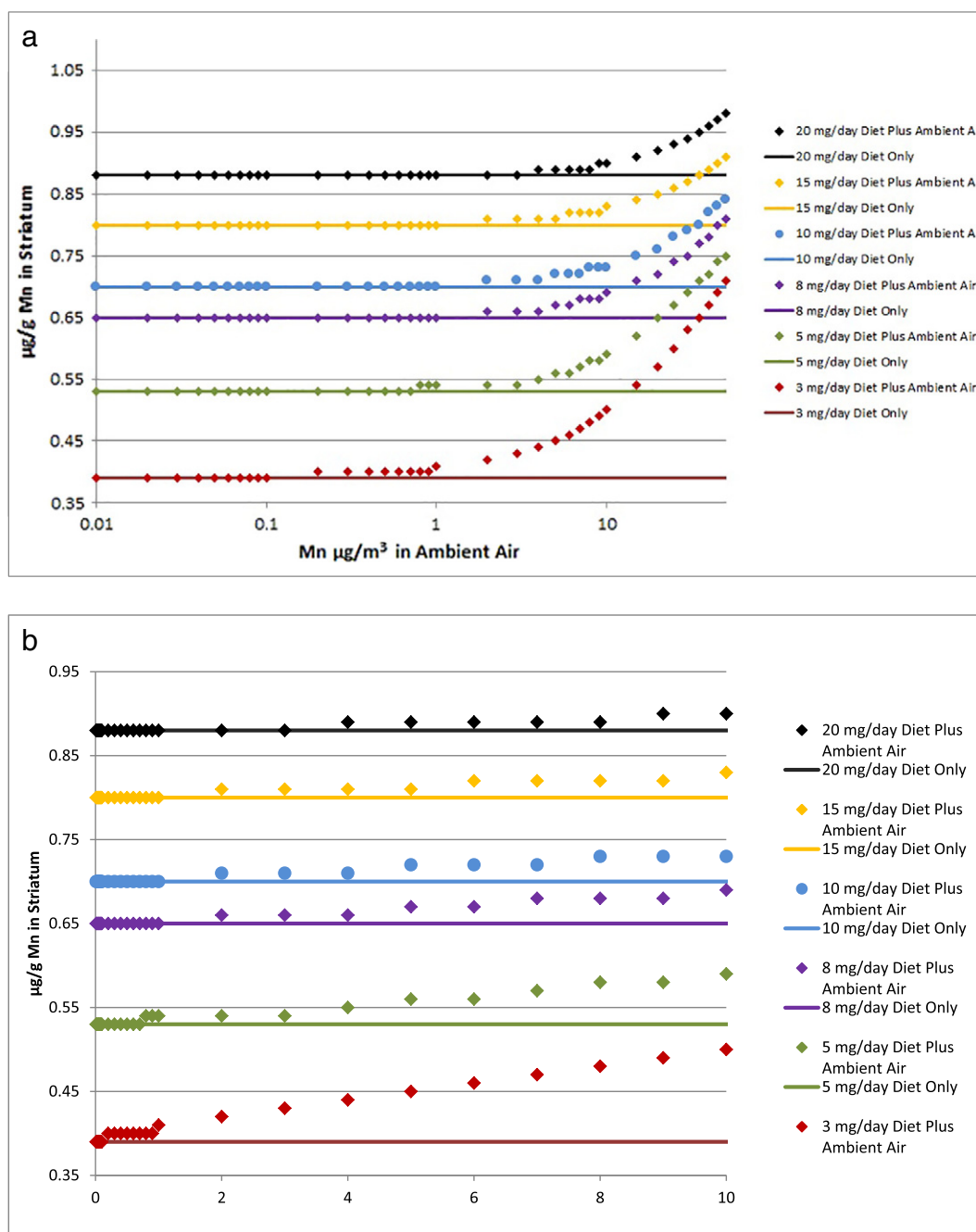


**Fig. 9.** a. Model-predicted concentration of Mn ( $\mu\text{g/g}$ ) in the globus pallidus (striatum) from exposure to various daily dietary Mn levels, or dietary Mn daily intake plus various ambient air levels of respirable Mn. Figure is based on a 70 kg human with exposure for 10 years at the indicated dietary intake. b. Model-predicted concentration of Mn ( $\mu\text{g/g}$ ) in the globus pallidus (striatum) from exposure to various daily dietary Mn levels, or dietary daily intake plus low ambient air levels of respirable Mn. Figure is based on a 70 kg human with exposure for 10 years at the indicated dietary intake.

an attempt to describe homeostatic controls of Mn during human development when challenged with overexposure to Mn. Mn plays a central role in normal prenatal and neonatal development and its deficiency may cause developmental deficits, such as abnormal brain function (Yoon et al., 2011). These life-stage PBPK models showed that adult males achieved a higher daily dose-to-target tissue than fetal, neonatal, pregnant, and non-pregnant female life-stages (Yoon et al., 2011). Based on these pharmacokinetic results, early life stages would be expected to have lower target tissue concentrations, therefore, no sensitive subpopulation adjustment would be necessary when basing risk assessments on occupational studies of adult males exposed to Mn (Taylor et al., 2012).

The potential variability in dietary intake of Mn on target tissue concentrations also needs to be considered when assessing the effects of inhaled Mn. A sensitivity analysis was conducted to determine the parameters that have the most significant impact on the estimation of Mn tissue concentrations in the globus pallidus when the human PBPK model was developed (Schroeter et al., 2011). At low Mn concentrations, the parameters having the largest impact were the influx and efflux diffusion rate constants into the brain, changes in dietary absorption and biliary excretion. Model predictions became less sensitive to dietary absorption and biliary excretion with increasing Mn inhalation exposure concentrations, because brain Mn levels were driven more by inhalation than diet. This observation demonstrates the importance

of any assumptions regarding dietary intake/absorption and biliary excretion in the estimation of changes in target tissue concentrations based on the contribution of inhalation exposure, as well as setting a target tissue NOAEL in occupational studies.

An average dietary intake of 3 mg/day Mn (slightly higher than the “adequate intake” level [Aschner and Aschner, 2005](#)), was applied in the human PBPK model for the current study. However, data from both the US ([CDC, 2010, 2012](#)) and Canada ([Health Canada, 2011](#)) indicate that average dietary intake of Mn varies from 2–6 mg/day in adults depending on the age range, with maximum intake up to 60–75 mg/day for individuals taking dietary supplements. These dietary intake values can significantly change the baseline target tissue concentration ([Fig. 9a](#)), particularly when considering the low Mn concentrations anticipated in ambient air ([Fig. 9b](#)). Analyses reported by [Schroeter et al. \(2011\)](#) demonstrated that PBPK model predictions became less sensitive to dietary absorption and biliary excretion with increasing Mn inhalation exposure concentrations, because brain Mn levels were driven more by inhalation than diet at higher air concentrations. Thus, dietary intake, rather than Mn air concentration, may be a dominant factor in determining target tissue concentration following exposure to low air concentrations, and thus, a likely determining factor in human variability of background Mn tissue concentrations.

Multiple occupational studies were evaluated using the human PBPK model for Mn to estimate tissue concentrations from corresponding air concentrations to derive the air concentrations associated with NOAELs. Two studies were negative for health outcomes ([Gibbs et al., 1999](#); [Myers et al., 2003a](#)), so the highest Mn air concentrations from these studies were used. All of the estimates of Mn target tissue concentrations were 0.7–1.0  $\mu\text{g/g}$  with corresponding air concentrations based on a typical workday of 200  $\mu\text{g}/\text{m}^3$ –1000  $\mu\text{g}/\text{m}^3$ . The PBPK model was also used to estimate the continuous inhalation exposure expected to cause these Mn target tissue concentrations. The modeled air concentrations of 50  $\mu\text{g}/\text{m}^3$ –150  $\mu\text{g}/\text{m}^3$  are compared to measured ambient Mn concentrations for Canada and the US to derive a MOS. The estimated MOS of 2500–12,000 suggest how much of an increase in ambient concentrations would be required to produce target tissue concentrations associated with the NOAEL for subclinical neurological effects.

The PBPK model for Mn may also be used to estimate inhaled concentrations required to cause increases in target tissues above background. This point of inflection falls in the ambient air range from 1 to 10  $\mu\text{g Mn}/\text{m}^3$  ([Table 3](#)). The model may also be used to estimate the target tissue concentration and corresponding air concentration corresponding to a NOAEL. Our simulations show that tissue concentration at the point of inflection is substantially below target tissue Mn associated with changes in subclinical neurological test results in occupational exposures ([Roels et al., 1992](#)). For instance, a recent study in welders indicated that plasma Mn (P-Mn) does not increase until the respirable Mn levels reach 10  $\mu\text{g}/\text{m}^3$  ([Hoet et al., 2012](#)). This observation, combined with the results of the current analysis, suggest that a Mn TLV-TWA larger than the currently recommended value of 20  $\mu\text{g}/\text{m}^3$  for respirable dust ([ACGIH, 2012](#)) could be relied upon and still be health protective.

In summary, the results of studies on Mn pharmacokinetics demonstrate that homeostatic mechanisms regulate the levels of Mn in the body from inhalation. Increases in target tissues above background occur only when humans (regardless of their age or gender) are exposed to air Mn concentrations far higher than those historically or currently measured in Canada or the US. These findings suggest that regulatory air Mn guidelines are extremely conservative and that the application of standard safety factors may not represent alterations in tissue delivery of Mn due to the nonlinearities in biological processes.

The current human PBPK models ([Schroeter et al., 2011](#); [Yoon et al., 2011](#)) are calibrated for adults or infants during gestation and lactation, and have not been extended to specifically address potential differences in children. Therefore, development of a model with pharmacokinetic values specific to children would be of value in addressing the need

for an uncertainty factor to extrapolate from adults to children. However, it is expected that children will display similar pharmacokinetics to adults—with significant background tissue levels of Mn that change very little with exposures until reaching 10  $\mu\text{g}/\text{m}^3$ . Questions regarding the potential for Mn to affect brain development and cognitive function might be addressed by extension of the model during gestation and lactation to evaluate potential changes in the cerebral cortex as the target tissue. Nonetheless, the globus pallidus is the most sensitive brain region regarding Mn accumulation, and is thus likely an appropriate surrogate for tissue level changes in the frontal cortex ([Dorman et al., 2006a, 2006b](#)). While the results of PBPK modeling have indicated critical parameters in estimating Mn target tissue concentrations, a Monte Carlo analysis for selected parameters in the PBPK model, in particular dietary variability among children and adults, would help refine the model estimates and more clearly evaluate the contribution of such factors as dietary exposure versus inhalation exposure in the low exposure regions.

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## Conflict of interest statement

The authors declare that there are no conflicts of interest and have read and understood the Conflict of Interest Policy from for the Journal.

## Transparency document

The [Transparency document](#) associated with this article can be found, in online version.

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## Appendix A. Supplementary data

Information on the determination of the amount of Mn consumed by an individual in their diet and through the use of supplements is presented as supplementary data. Additionally, the determination of the ambient air concentration of Mn inhaled by an individual is also presented as supplementary material. This information is published online. Supplementary data associated with this article can be found in the online version, at [10.1016/j.taap.2017.02.015](https://doi.org/10.1016/j.taap.2017.02.015).

## References

- ACGIH, 2012. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati.
- Andersen, M.E., Gearhart, J.M., Clewell III, H.J., 1999. Pharmacokinetic data needs to support risk assessments for inhaled and ingested manganese. *Neurotoxicology* 20 (2–3), 161–172.
- Andersen, M.E., Dorman, D.C., Clewell 3rd, H.J., Taylor, M.D., Nong, A., 2010. Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment. *J. Toxicol. Environ. Health* 73 (2), 217–234.
- Armitage, P., 1955. Tests for linear trends in proportions and frequencies. *Biometrics* 11 (3), 375–386.
- Aschner, J.L., Aschner, M., 2005. Nutritional aspects of manganese homeostasis. *Mol. Asp. Med.* 26 (4–5), 353–362.
- ATSDR, 2012. Toxicological Profile for Manganese. Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services September 2012. <http://www.atsdr.cdc.gov/ToxProfiles/tp151.pdf>.



- Barton, H.A., Clewell 3rd, H.J., 2000. Evaluating noncancer effects of trichloroethylene: dosimetry, mode of action, and risk assessment. *Environ. Health Perspect.* 108 (Suppl. 2), 323–334.
- Bast-Petersen, R., Ellingsen, D.G., Hetland, S.M., Thomassen, Y., 2004. Neuropsychological function in manganese alloy plant workers. *Int. Arch. Occup. Environ. Health* 77 (4), 277–287.
- Bouchard, M., Mergler, D., Baldwin, M., Panisset, M., Bowler, R., Roels, H.A., 2007a. Neurobehavioral functioning after cessation of manganese exposure: a follow-up after 14 years. *Am. J. Ind. Med.* 50 (11), 831–840.
- Bouchard, M., Mergler, D., Baldwin, M., Panisset, M., Roels, H.A., 2007b. Neuropsychiatric symptoms and past manganese exposure in a ferro-alloy plant. *Neurotoxicology* 28 (2), 290–297.
- Bush, V.J., Moyer, T.P., Batts, K.P., Parisi, J.E., 1995. Essential and toxic element concentrations in fresh and formalin-fixed human autopsy tissues. *Clin. Chem.* 41 (2), 284–294.
- CDC, 2006. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey. Analytic and Reporting Guidelines. The National Health and Nutrition Examination Survey (NHANES). U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, MD September, 2006. Available at: [http://www.cdc.gov/nchs/nhanes/nhanes\\_questionnaires.htm](http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm).
- CDC, 2007. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, MD 2003–2006. Available at: [http://www.cdc.gov/nchs/nhanes/nhanes\\_questionnaires.htm](http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm).
- CDC, 2010. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, MD Demographics Data 2009–2010. Available at: [http://www.cdc.gov/nchs/nhanes/nhanes\\_questionnaires.htm](http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm).
- CDC, 2012. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, MD Demographics Data 2011–2012. Available at: [http://www.cdc.gov/nchs/nhanes/nhanes\\_questionnaires.htm](http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm).
- Clewell 3rd, H.J., Andersen, M.E., 1985. Risk assessment extrapolations and physiological modeling. *Toxicol. Ind. Health* 1 (4), 111–131.
- Clewell, H.J., Gentry, P.R., Gearhart, J.M., Allen, B.C., Andersen, M.E., 1995. Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: examples with vinyl chloride and trichloroethylene. *Chemosphere* 31 (1), 2561–2578.
- Cochran, W., 1954. Some methods for strengthening the common  $X^2$  tests. *Biometrics* 10 (4), 417–451.
- Dastur, D.K., Manghani, D.K., Raghavendran, K.V., 1971. Distribution and fate of Mn in the monkey: studies of different parts of the central nervous system and other organs. *J. Clin. Invest.* 50 (1), 9–20.
- Davidsson, L., Cederblad, A., Hagebo, E., Lonnerdal, B., Sandstrom, B., 1988. Intrinsic and extrinsic labeling for studies of manganese absorption in humans. *J. Nutr.* 118 (12), 1517–1521.
- Deschamps, F.J., Guillaumot, M., Raux, S., 2001. Neurological effects in workers exposed to manganese. *J. Occup. Environ. Med.* 43 (2), 127–132.
- Dorman, D.C., Struve, M.F., James, R.A., Marshall, M.W., Parkinson, C.U., Wong, B.A., 2001. Influence of particle solubility on the delivery of inhaled manganese to the rat brain: manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure. *Toxicol. Appl. Pharmacol.* 170 (2), 79–87.
- Dorman, D.C., Struve, M.F., Marshall, M.W., Parkinson, C.U., James, R.A., Wong, B.A., 2006a. Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. *Toxicol. Sci.* 92 (1), 201–210.
- Dorman, D.C., Struve, M.F., Wong, B.A., Dye, J.A., Robertson, I.D., 2006b. Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. *Toxicol. Sci.* 92 (1), 219–227.
- Dorman, D.C., Andersen, M.E., Roper, J.M., Taylor, M.D., 2012. Update on a pharmacokinetic-centric Alternative Tier II Program for MMT—part I: program implementation and lessons learned. *J. Toxicol.* 2012, 946742.
- Eriksson, H., Tedroff, J., Thuomas, K.A., Aquilonius, S.M., Hartvig, P., Fasth, K.J., Bjurling, P., Langström, B., Hedström, K.G., Heilbron, E., 1992. Manganese induced brain lesions in *Macaca fascicularis* as revealed by positron emission tomography and magnetic resonance imaging. *Arch. Toxicol.* 66 (6), 403–407.
- Fittro, K.P., Bolla, K.I., Heller, J.R., Meyd, C.J., 1992. The Milan Automated Neurobehavioral System. Age, sex, and education differences. *J. Occup. Med.* 34 (9), 918–922.
- Furchner, J.E., Richmond, C.R., Drake, G.A., 1966. Comparative metabolism of radionuclides in mammals. III. Retention of manganese-54 in the mouse, rat, monkey, and dog. *Health Phys.* 12 (10), 673–675.
- Gibbs, J.P., Crump, K.S., Houck, D.P., Warren, P.A., Mosley, W.S., 1999. Focused medical surveillance: a search for subclinical movement disorders in a cohort of U.S. workers exposed to low levels of manganese dust. *Neurotoxicology* 20 (2–3), 299–313.
- Guilarte, T.R., 2010. Manganese and Parkinson's disease: a critical review and new findings. *Environ. Health Perspect.* 118 (8), 1071–1080.
- Guilarte, T.R., 2013. Manganese neurotoxicity: new perspectives from behavioral, neuroimaging, and neuropathological studies in humans and non-human primates. *Front. Aging Neurosci.* 5, 1–10 Article 23.
- Gwiazda, R., Lucchini, R., Smith, D., 2007. Adequacy and consistency of animal studies to evaluate the neurotoxicity of chronic low-level manganese exposure in humans. *J. Toxicol. Environ. Health A* 70 (7), 594–605.
- Health Canada, 2010. Human Health Risk Assessment for Inhaled Manganese. Prepared by: Water, Air and Climate Change Bureau Healthy Environments and Consumer Safety Branch.
- Health Canada, 2011. Trace Elements Table: Average Dietary Intakes ( $\mu\text{g/kg bw/day}$ ) of Trace Elements for Canadians in Different Age/Sex Groups for Total Diet Study in 2007. (Last Updated: January 31, 2011. Available at: [http://www.hc-sc.gc.ca/fn-an/surveill/total-diet/intake-apport/index-eng.php?\\_sm\\_au\\_=iV4Z1W6r2nQvSP6](http://www.hc-sc.gc.ca/fn-an/surveill/total-diet/intake-apport/index-eng.php?_sm_au_=iV4Z1W6r2nQvSP6). Accessed September 2015).
- Hoet, P., Vanmarcke, E., Geens, T., Deumer, G., Haufroid, V., Roels, H.A., 2012. Manganese in plasma: a promising biomarker of exposure to Mn in welders. A pilot study. *Toxicol. Lett.* 213 (1), 69–74.
- Leavens, T.L., Rao, D., Andersen, M.E., Dorman, D.C., 2007. Evaluating transport of manganese from olfactory mucosa to striatum by pharmacokinetic modeling. *Toxicol. Sci.* 97 (2), 265–278.
- Lee, W.Y., Iannucci-Berger, W.A., Eitzer, B.D., White, J.C., Mattina, M.J., 2003. Plant uptake and translocation of air-borne chlordane and comparison with the soil-to-plant route. *Chemosphere* 53 (2), 111–121.
- Lees-Haley, P.R., Rohling, M.L., Langhinrichsen-Rohling, J., 2006. A meta-analysis of the neuropsychological effects of occupational exposure to manganese. *Clin. Neuropsychol.* 20 (1), 90–107.
- Lucchini, R., Selis, L., Folli, D., Apostoli, P., Vanoni, O., Iregren, A., Alessio, L., 1995. Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure. *Scand. J. Work Environ. Health* 21 (2), 143–149.
- Lucchini, R., Bergamaschi, E., Smargiassi, A., Festa, D., Apostoli, P., 1997. Motor function, olfactory threshold, and hematological indices in manganese-exposed ferroalloy workers. *Environ. Res.* 73 (1–2), 175–180.
- Lucchini, R., Apostoli, P., Perrone, C., Placidi, D., Albin, E., Migliorati, P., Mergler, D., Sassine, M.P., Palmi, S., Alessio, L., 1999. Long term exposure to “low levels” of manganese oxides and neurofunctional changes in ferroalloy workers. *Neurotoxicology* 20 (2–3), 287–298.
- Mahoney, J.P., Small, W.J., 1968. Studies on manganese III. The biological half-life of radiomanganese in man and factors which affect this half-life. *J. Clin. Invest.* 47 (3), 643–653.
- Mena, I., Marin, O., Fuenzalida, S., Cotzias, G.C., 1967. Chronic manganese poisoning: clinical picture and manganese turnover. *Neurology* 17 (2), 128–136.
- Mergler, D., Huel, G., Bowler, R., Iregren, A., Belanger, S., Baldwin, M., Tardif, R., Smargiassi, A., Martin, L., 1994. Nervous system dysfunction among workers with long-term exposure to manganese. *Environ. Res.* 64 (2), 151–180.
- Myers, J.E., Thompson, M.L., Naik, I., Theodorou, P., Esswein, E., Tassell, H., Daya, A., Renton, K., Spies, A., Paicker, J., Young, T., Jeebhay, M., Ramushu, S., London, L., Rees, D.J., 2003a. The utility of biological monitoring for manganese in ferroalloy smelter workers in South Africa. *Neurotoxicology* 24 (6), 875–883.
- Myers, J.E., Thompson, M.L., Ramushu, S., Young, T., Jeebhay, M.F., London, L., Esswein, E., Renton, K., Spies, A., Boule, A., Naik, I., Iregren, A., Rees, D.J., 2003b. The nervous system effects of occupational exposure on workers in a South African manganese smelter. *Neurotoxicology* 24 (6), 885–894.
- Myers, J.E., teWaterNaude, J., Fourie, M., Zogoe, H.B., Naik, I., Theodorou, P., Tassell, H., Daya, A., Thompson, M.L., 2003c. Nervous system effects of occupational manganese exposure on South African manganese mineworkers. *Neurotoxicology* 24 (4–5), 649–656.
- NAPS, 2015. National Air Pollution Surveillance Network. (Available at: <http://www.ec.gc.ca/natchem/default.asp?lang=en&n=E0E2169-1>. Last accessed September 2015).
- Newland, M.C., Cox, C., Hamada, R., Oberdorster, G., Weiss, B., 1987. The clearance of manganese chloride in the primate. *Fundam. Appl. Toxicol.* 9 (2), 314–328.
- Newland, M.C., Cecklet, T.L., Kordower, J.H., Weiss, B., 1989. Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. *Exp. Neurol.* 106 (3), 251–258.
- Nong, A., Teeguarden, J.G., Clewell 3rd, H.J., Dorman, D.C., Andersen, M.E., 2008. Pharmacokinetic modeling of manganese in the rat. IV: assessing factors that contribute to brain accumulation during inhalation exposure. *J. Toxicol. Environ. Health* 71 (7), 413–426.
- Nong, A., Taylor, M.D., Clewell 3rd, H.J., Dorman, D.C., Andersen, M.E., 2009. Manganese tissue dosimetry in rats and monkeys: accounting for dietary and inhaled Mn with physiologically based pharmacokinetic modeling. *Toxicol. Sci.* 108 (1), 22–34.
- Olanow, C.W., Good, P.F., Shinotoh, H., Hewitt, K.A., Vingerhoets, F., Snow, B.J., Beal, M.F., Caine, D.B., Perl, D.P., 1996. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. *Neurology* 46 (2), 492–498.
- Roels, H., 1993. Correspondence from H. Roels. Faculté de Médecine, Unité de Toxicologie et Médecine du Travail, Catholique Université de Louvain, Clos Chapelle-aux-Champs 30, BTE 3054, 1200 Bruxelles, Belgium, to J. Michael Davis, Environmental Criteria and Assessment Office (MD-52). U.S. EPA, Research Triangle Park, NC 27711 (October 19. As cited in USEPA 1993).
- Roels, H., Lauwerys, R., Genet, P., Sarhan, M.J., de Fays, M., Hanotiau, I., Buchet, J.P., 1987a. Relationship between external and internal parameters of exposure to manganese in workers from a manganese oxide and salt producing plant. *Am. J. Ind. Med.* 11 (3), 297–305.
- Roels, H., Lauwerys, R., Buchet, J.P., Genet, P., Sarhan, M.J., Hanotiau, I., de Fays, M., Bernard, A., Stanesco, D., 1987b. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. *Am. J. Ind. Med.* 11 (3), 307–327.
- Roels, H.A., Ghyselen, P., Buchet, J.P., Ceulemans, E., Lauwerys, R.R., 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Br. J. Ind. Med.* 49 (1), 25–34.
- Roels, H.A., Ortega Eslava, M.I., Ceulemans, E., Robert, A., Lison, D., 1999. Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. *Neurotoxicology* 20 (2–3), 255–271.
- Roels, H.A., Bowler, R.M., Kim, Y., Claus Henn, B., Mergler, D., Hoet, P., Gocheva, V.V., Bellinger, D.C., Wright, R.O., Harris, M.G., Chang, Y., Bouchard, M.F., Rioias-Rodriguez, H., Menezes-Filho, J.A., Tellez-Rojas, M.M., 2012. Manganese exposure and cognitive deficits: a growing concern for manganese neurotoxicity. *Neurotoxicology* 33 (4), 872–880.

- Schroeter, J.D., Kimbell, J.S., Gross, E.A., Willson, G.A., Dorman, D.C., Tan, Y.M., Clewell III, H.J., 2008. Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein. *Inhal. Toxicol.* 20 (3), 227–243.
- Schroeter, J.D., Nong, A., Yoon, M., Taylor, M.D., Dorman, D.C., Andersen, M.E., Clewell 3rd, H.J., 2011. Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multi-route physiologically based pharmacokinetic models. *Toxicol. Sci.* 120 (2), 481–498.
- Schroeter, J.D., Dorman, D.C., Yoon, M., Nong, A., Taylor, M.D., Andersen, M.E., Clewell 3rd, H.J., 2012. Application of a multi-route physiologically based pharmacokinetic model for manganese to evaluate dose-dependent neurological effects in monkeys. *Toxicol. Sci.* 129 (2), 432–446.
- Taylor, M.D., Clewell 3rd, H.J., Andersen, M.E., Schroeter, J.D., Yoon, M., Keene, A.M., Dorman, D.C., 2012. Update on a pharmacokinetic-centric Alternative Tier II Program for MMT—part II: physiologically based pharmacokinetic modeling and manganese risk assessment. *J. Toxicol.* 2012, 791431.
- Teeguarden, J.G., Dorman, D.C., Covington, T.R., Clewell 3rd, H.J., Andersen, M.E., 2007a. Pharmacokinetic modeling of manganese. I. Dose dependencies of uptake and elimination. *J. Toxicol. Environ. Health* 70 (18), 1493–1504.
- Teeguarden, J.G., Dorman, D.C., Nong, A., Covington, T.R., Clewell 3rd, H.J., Andersen, M.E., 2007b. Pharmacokinetic modeling of manganese. II. Hepatic processing after ingestion and inhalation. *J. Toxicol. Environ. Health* 70 (18), 1505–1514.
- Teeguarden, J.G., Gearhart, J., Clewell 3rd, H.J., Covington, T.R., Nong, A., Andersen, M.E., 2007c. Pharmacokinetic modeling of manganese. III. Physiological approaches accounting for background and tracer kinetics. *J. Toxicol. Environ. Health* 70 (18), 1515–1526.
- Tukey, J.W., Ciminera, J.L., Heyse, J.F., 1985. Testing the statistical certainty of a response to increasing doses of a drug. *Biometrics* 41 (1), 295–301.
- USDA, 2012. USDA Food and Nutrient Database for Dietary Studies 2011–2012. Food Surveys Research Group Home Page. U.S. Department of Agriculture, Agricultural Research Service Available at: <http://www.ars.usda.gov/ba/bhnrc/fsrg>.
- USDA, 2014. USDA National Nutrient Database for Standard Reference, Release 27. (Version Current: August 2014. Available at: <http://www.ars.usda.gov/ba/bhnrc/ndl>. Accessed September 2015).
- USEPA, 1993. Manganese (CASRN 7439-96-5). Inhalation RfC Assessment. United States Environmental Protection Agency (Available at: <http://www.epa.gov/iris/subst/0373.htm>. Last Accessed April, 2016).
- USEPA, 1998. Integrated Risk Information System (IRIS): Manganese (CASRN 7439-96-5). United States Environmental Protection Agency Available at: [http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance\\_nmbr=0373](http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=0373).
- USEPA, 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. United States Environmental Protection Agency, Washington, D.C. (EPA/630/P-03/001F).
- USEPA, 2006. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. National Center for Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington, D.C. (EPA/600/R-05/043F).
- USEPA, 2015. Technology Transfer Network (TTN) Air Quality System (AQS) Data Mart. United States Environmental Protection Agency Available at: [https://aqsweb.epa.gov/aqsweb/documents/data\\_mart\\_welcome.html](https://aqsweb.epa.gov/aqsweb/documents/data_mart_welcome.html).
- Vitarella, D., Moss, O., Dorman, D.C., 2000. Pulmonary clearance of manganese phosphate, manganese sulfate, and manganese tetraoxide by CD rats following intratracheal instillation. *Inhal. Toxicol.* 12 (10), 941–957.
- Yoon, M., Nong, A., Clewell 3rd, H.J., Taylor, M.D., Dorman, D.C., Andersen, M.E., 2009a. Evaluating placental transfer and tissue concentrations of manganese in the pregnant rat and fetuses after inhalation exposures with a PBPK model. *Toxicol. Sci.* 112 (1), 44–58.
- Yoon, M., Nong, A., Clewell 3rd, H.J., Taylor, M.D., Dorman, D.C., Andersen, M.E., 2009b. Lactational transfer of manganese in rats: predicting manganese tissue concentration in the dam and pups from inhalation exposure with a pharmacokinetic model. *Toxicol. Sci.* 112 (1), 23–43.
- Yoon, M., Schroeter, J.D., Nong, A., Taylor, M.D., Dorman, D.C., Andersen, M.E., Clewell 3rd, H.J., 2011. Physiologically based pharmacokinetic modeling of fetal and neonatal manganese exposure in humans: describing manganese homeostasis during development. *Toxicol. Sci.* 122 (2), 297–316.
- Young, T., Myers, J.E., Thompson, M.L., 2005. The nervous system effects of occupational exposure to manganese—measured as respirable dust—in a South African manganese smelter. *Neurotoxicology* 26 (6), 993–1000.

**ATTACHMENT D**

**Schroeter et al. (2011)**  
**Yoon et al. (2019)**  
**Campbell et al. (2022)**



# Analysis of Manganese Tracer Kinetics and Target Tissue Dosimetry in Monkeys and Humans with Multi-Route Physiologically Based Pharmacokinetic Models

Jeffrey D. Schroeter,<sup>\*,1</sup> Andy Nong,<sup>\*</sup> Miyoung Yoon,<sup>\*</sup> Michael D. Taylor,<sup>†</sup> David C. Dorman,<sup>‡</sup> Melvin E. Andersen,<sup>\*</sup> and Harvey J. Clewell, III<sup>\*</sup>

<sup>\*</sup>The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709-2137; <sup>†</sup>Afton Chemical Corp., Richmond, Virginia 23219; and <sup>‡</sup>College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606

<sup>1</sup>To whom correspondence should be addressed at The Hamner Institutes for Health Sciences, 6 Davis Drive, Research Triangle Park, NC 27709-2137. Fax: (919) 558-1300. E-mail: jschroeter@thehamner.org.

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Manganese (Mn) is an essential nutrient with the capacity for toxicity from excessive exposure. Accumulation of Mn in the striatum, globus pallidus, and other midbrain regions is associated with neurotoxicity following high-dose Mn inhalation. Physiologically based pharmacokinetic (PBPK) models for ingested and inhaled Mn in rats and nonhuman primates were previously developed. The models contained saturable Mn tissue-binding capacities, preferential fluxes of Mn in specific tissues, and homeostatic control processes such as inducible biliary excretion of Mn. In this study, a nonhuman primate model was scaled to humans and was further extended to include iv, ip, and sc exposure routes so that past studies regarding radiolabeled carrier-free <sup>54</sup>MnCl<sub>2</sub> tracer kinetics could be evaluated. Simulation results accurately recapitulated the biphasic elimination behavior for all exposure routes. The PBPK models also provided consistent cross-species descriptions of Mn tracer kinetics across multiple exposure routes. These results indicate that PBPK models can accurately simulate the overall kinetic behavior of Mn and predict conditions where exposures will increase free Mn in various tissues throughout the body. Simulations with the human model indicate that globus pallidus Mn concentrations are unaffected by air concentrations < 10 µg/m<sup>3</sup> Mn. The use of this human Mn PBPK model can become a key component of future human health risk assessment of Mn, allowing the consideration of various exposure routes, natural tissue background levels, and homeostatic controls to explore exposure conditions that lead to increased target tissue levels resulting from Mn overexposure.

**Key Words:** manganese; PBPK; inhalation exposure; risk assessment; neurotoxicity; pharmacokinetics.

The essential trace element manganese (Mn) is found in all human tissues and is required for numerous physiological processes, including protein and carbohydrate metabolism, immune system function, and bone growth. The primary source of Mn exposure is through the diet, with adult human

consumption ranging from 1 to 10 mg Mn/day, of which approximately 1–5% is absorbed by the gastrointestinal (GI) tract (Aschner *et al.*, 2005; ATSDR, 2000; Freeland-Graves, 1994). Homeostatic controls tightly restrict Mn absorption and regulate Mn excretion to maintain stable tissue levels despite fluctuations in daily Mn dietary exposure.

Neurotoxicity can occur when Mn intake exceeds elimination resulting in Mn accumulation in midbrain regions that influence motor control such as the globus pallidus, striatum, and substantia nigra (Dorman *et al.*, 2006b; Yamada *et al.*, 1986). Similar neurological responses have been linked to prolonged high-dose Mn inhalation (Pal *et al.*, 1999) or drinking water ingestion (Kawamura *et al.*, 1941), impaired Mn clearance because of liver dysfunction (Spahr *et al.*, 1996), and long-term parenteral nutrition (Fell *et al.*, 1996). To understand the risk to humans from excessive Mn exposure, it is important to determine the exposure conditions that result in Mn concentrations in the brain that are increased significantly compared with brain Mn concentrations arising from normal dietary intake (Andersen *et al.*, 1999).

Inhalation has historically been the exposure route of most concern for Mn because inhaled Mn particles that deposit on lung epithelium bypass uptake control in the GI tract and liver and directly enter the systemic circulation. Prolonged exposure to high levels (> 1 mg/m<sup>3</sup>) of Mn-laden dusts in occupational settings such as mining can result in severe Mn-induced neurotoxicity, including the onset of manganism, an extrapyramidal movement disorder that is similar but clinically distinguishable from Parkinson's disease (Aschner *et al.*, 2005; Pal *et al.*, 1999). Neurological effects of a subclinical nature have been reported in workers with chronic inhalation to lower concentrations (0.5–1.0 mg/m<sup>3</sup>) of Mn in the workplace (Iregren, 1990; Lucchini *et al.*, 1995, 1999; Mergler *et al.*, 1994; Myers *et al.*, 2003; Roels, *et al.*, 1987, 1992, 1999; Young *et al.*, 2005). Other studies have indicated that

environmental exposures may also be associated with subtle, subclinical neurological changes in the general population (Finkelstein and Jerrett, 2007; Lucchini *et al.*, 2007; Mergler *et al.*, 1999; Rodriguez-Agudelo *et al.*, 2006).

Concerns regarding chronic low-level Mn inhalation exposure have led to the development of an extensive Mn pharmacokinetic data set and physiologically based pharmacokinetic (PBPK) models. This series of pharmacokinetic modeling studies described Mn kinetics using compartmental models (Teeguarden *et al.*, 2007a,b,c), PBPK models of adult rats and monkeys (Nong *et al.*, 2008, 2009), and PBPK models of gestation and lactation in rats (Yoon *et al.*, 2009a,b). The first Mn compartmental pharmacokinetic models used linear exchange rates to simulate Mn tissue kinetics under normal and deficient dietary conditions but were unable to capture the rapid rise in tissue Mn concentrations seen during inhalation exposure to high Mn concentrations. An enhanced model structure allowed tissue compartments to retain fairly constant Mn levels during normal dietary intake and included saturable Mn tissue stores that increased rapidly under inhalation exposure conditions (Nong *et al.*, 2009). These PBPK modeling efforts produced a consistent description of Mn tissue kinetics in rats and monkeys following dietary and inhalation exposures (Andersen *et al.*, 2010).

In the current study, the previous PBPK model for rats and monkeys (Nong *et al.*, 2009) was extended to humans to predict inhalation exposure conditions that result in increased brain Mn concentrations. In addition, multiple exposure routes were examined, including iv, ip, and sc injection, to simulate distribution and elimination of the radioisotope  $^{54}\text{Mn}$ . The addition of these exposure routes allowed analysis of studies that have been conducted to analyze tracer kinetics of  $^{54}\text{Mn}$  in nonhuman primates and human volunteers. These studies are important to consider because activity of the soluble, carrier-free  $^{54}\text{Mn}$  (given as  $^{54}\text{MnCl}_2$ ) implicitly reflects the overall kinetics of Mn in the body.

## MATERIALS AND METHODS

**PBPK model structure.** The PBPK model structure contained compartments for the liver, lung, nasal cavity, bone, blood, cerebellum, olfactory bulb, globus pallidus, and pituitary gland (Fig. 1). Remaining body tissues were combined into a single compartment. The same model structure was used for monkeys and humans. A thorough description of the model parameters and underlying equations are given in Nong *et al.* (2008, 2009). The model simulates concurrent exposure to dietary and inhaled Mn and also simulates  $^{54}\text{Mn}$  tracer kinetics from oral and inhalation exposure and by ip, iv, and sc administration.

Inhalation exposure was to  $\text{MnSO}_4$  particles, which are highly soluble in mucus and tissue (Vitarella *et al.*, 2000). Aerosol parameters for  $\text{MnSO}_4$  consisted of a mass median aerodynamic diameter of 2.0  $\mu\text{m}$ , a geometric SD of 1.5 and a particle density of 2.95  $\text{g}/\text{cm}^3$  (Dorman *et al.*, 2006a). Fractional deposition of inhaled  $\text{MnSO}_4$  particles in the respiratory tract was calculated using the Multiple-Path Particle Dosimetry model (MPPD version 2.0; Anjilvel and Asgharian, 1995; Asgharian *et al.*, 2001; available at <http://www.thehamner.org>). Nasal deposition estimates from the MPPD model were partitioned onto the respiratory and olfactory epithelium based on species-

dependent airflow allocation (Kepler *et al.*, 1998; Schroeter *et al.*, 2010). Deposited Mn was assumed to be rapidly absorbed from lung tissues and nasal respiratory epithelium into the systemic circulation or transported from the nasal olfactory epithelium to the olfactory bulb.

Absorption of Mn by the GI tract is dose dependent. As dietary Mn levels increase, GI absorption decreases and biliary excretion increases (Dorman *et al.*, 2001b; Teeguarden *et al.*, 2007b). These homeostatic controls are overwhelmed when Mn exposure is high, leading to increases in free Mn tissue levels. The fraction of Mn absorbed by the GI tract ( $F_{\text{dietup}}$ ) and the biliary excretion rate constant ( $k_{\text{bilec}}$ ) were calibrated based on steady-state tissue concentrations and  $^{54}\text{Mn}$  whole-body elimination curves. Induction of biliary elimination of Mn was included to describe increased bile elimination that was directly observed in higher exposure concentrations in monkeys (Nong *et al.*, 2009). The biliary elimination rate constant was dependent on blood Mn concentration:

$$k_{\text{bile}} = k_{\text{bile0}} \left( 1 + \frac{k_{\text{bmax}} C_{\text{art}}^n}{k_{\text{b50}}^n + C_{\text{art}}^n} \right), \quad (1)$$

where  $k_{\text{bile0}}$  is the basal biliary excretion rate constant,  $k_{\text{bmax}}$  is the maximal increase in the excretion rate constant,  $k_{\text{b50}}$  is the arterial concentration at half the induced level of Mn in the arterial blood ( $C_{\text{art}}$ ), and  $n$  is the slope factor.  $C_{\text{art}}$  was used as a surrogate for free Mn liver concentrations, the presumed driver for Mn excretion, because Mn blood levels were directly measured in monkeys (Dorman *et al.*, 2006a; Nong *et al.*, 2009).

A simplified GI tract was used in the Mn PBPK model by Nong *et al.* (2009) because there was no need to track unabsorbed or absorbed Mn after it was excreted in the bile. Modifications were made to this GI structure to include fecal excretion (to be consistent with the data from Newland *et al.*, 1987) and simulate tracer kinetics of  $^{54}\text{Mn}$  administered orally in monkeys and humans. A series of gut compartments were added that were consistent with the physiology of Mn absorption by the GI tract (Fig. 1).  $F_{\text{dietup}}$  represents the fraction of dietary Mn that was absorbed in the GI tract and was available to the systemic circulation. This process was described as a direct transfer from the gut lumen to the liver. The remaining fraction of Mn ( $1 - F_{\text{dietup}}$ ) in the gut lumen was absorbed by the gut epithelium and stored in enterocytes or transferred to the lower GI tract lumen and excreted through the feces.  $F_{\text{ent}} \times k_{\text{GI}}$  represents the storage rate constant of the enterocytes in the gut epithelium, where  $F_{\text{ent}}$  is the fraction stored by the enterocytes and  $k_{\text{GI}}$  is the rate constant for movement from the gut lumen. Mn transfer from the gut epithelium to the lower GI tract was by sloughing of enterocytes ( $k_{\text{ent}}$ ) from the epithelial layer. The stored Mn in enterocytes was eventually excreted into feces without entering the systemic circulation because of enterocyte turnover. Mn elimination from the body through the feces was governed by the rate constant  $k_{\text{feces}}$ .

The following biologically informed assumptions were made concerning distribution of absorbed Mn. All tissues contain both free and bound Mn. Free Mn circulates in the blood throughout the body. Bound Mn is stored in tissue constituents where it participates in various physiological functions. Mn binding is a reversible, saturable process described by tissue-specific association ( $k_a$ ) and dissociation ( $k_d$ ) rate constants. The distribution between bound and free Mn is determined by the dissociation binding ratio ( $k_d/k_a$ ). The maximal binding capacity ( $B_{\text{max}}$ ) constrains the levels of bound Mn in each tissue; saturation of the binding capacity with increasing exposure concentration leads to increases in concentrations of free Mn in each tissue. The rate of change of free Mn in each tissue depends on their respective binding rate constants and maximal binding capacity.

Certain brain regions in monkeys exposed to higher doses of Mn by inhalation have preferential increases in tissue Mn (Dorman *et al.*, 2006a). Selective increases in brain Mn in some tissues following inhalation exposure could not be accurately simulated using only dissociation processes. Differential increases in free Mn in the four brain regions (globus pallidus, pituitary, cerebellum, and olfactory bulb) were described by asymmetric diffusion rate constants from tissue blood into tissue and back ( $k_{\text{in}}$  and  $k_{\text{out}}$ ). In addition, the globus pallidus and pituitary influx rates were modified by introducing a concentration-dependent influx rate constant (Nong *et al.*, 2009):

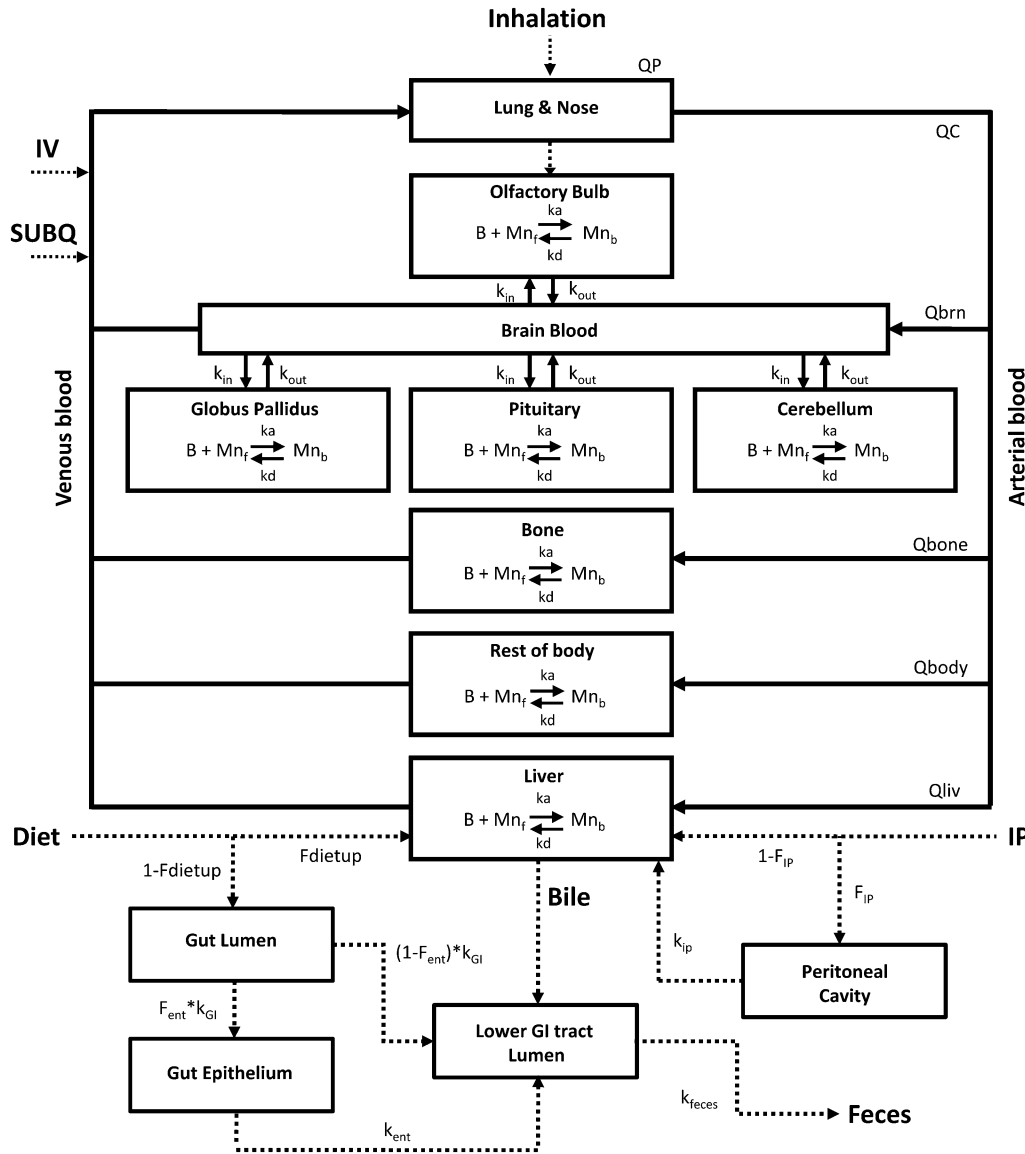


**FIG. 1.** The PBPK model structure describing Mn tissue kinetics in adult monkeys and humans. In each tissue compartment, the amount of bound Mn is in equilibrium with the assumed binding capacity ( $B_{tissue}$ ) and free Mn. Tissue-binding processes were controlled by association and dissociation rate constants ( $k_a$  and  $k_d$ ). Free Mn moves in the blood throughout the body and is stored in each tissue as bound Mn. Influx and efflux diffusion rate constants ( $k_{in}$  and  $k_{out}$ ) control preferential increases in free Mn in brain regions.  $Q_P$ ,  $Q_C$ , and  $Q_{tissue}$  refer to pulmonary ventilation, cardiac output, and tissue blood flows.

$$k_{in} = k_{in0} \left( 1 + \frac{k_{in \max} A_{free,t}}{k_{in50} + A_{free,t}} \right), \quad (2)$$

where  $k_{in0}$  is the basal influx rate constant,  $k_{in \max}$  is the maximal influx rate,  $k_{in50}$  is the affinity rate constant, and  $A_{free}$  is the amount of free Mn in the respective brain region. Defining an increase in tissue influx rate constant as free Mn increases was needed to describe changes in Mn concentrations in these brain regions that could not be sufficiently described by association and dissociation rate constants. The rate of change of free Mn in brain regions depends on diffusional clearance into and out of the tissues and on the binding rate constants and binding capacity in each tissue.

In addition to dietary and inhalation exposure routes, model components were included to account for administration of  $^{54}\text{Mn}$  by ip, iv, and sc injection (Fig. 1). Iv and sc injections were input directly into the venous blood; ip injections were simulated by placing the majority of the injected dose directly

into the liver, consistent with uptake by the highly vascularized GI tissue. A small fraction of the ip dose ( $F_{IP}$ ) was absorbed into the peritoneal cavity where it was slowly released ( $k_{IP}$ ) into the liver.

**Monkey model parameterization.** Physiological and anatomical parameters for the monkey PBPK model were obtained from Davies and Morris (1993), Dorman *et al.* (2006a), and Nong *et al.* (2009) (Table 1). A body weight of 2.5 kg was used in the monkey inhalation exposure simulations to be consistent with body weights reported by Dorman *et al.* (2006a). Basal Mn tissue levels (Table 2) were set to tissue measurements in control monkeys fed a commercial diet containing 133 ppm Mn (Dorman *et al.*, 2006a) by adjusting the parameters governing dietary absorption ( $F_{dietup}$ ) and biliary elimination ( $k_{bilec}$ ) (Table 3). Nasal and lung deposition fractions for the monkey were scaled from the rat by nasal epithelial surface area and pulmonary ventilation, respectively. As reported by Nong *et al.* (2009), Mn nasal and lung deposition values were 40 and 27%, respectively. Nasal deposition was further divided

TABLE 1

## Physiological Parameters for Monkeys and Humans

| Parameter                                                   | Monkey                  | Human  | Units                               |
|-------------------------------------------------------------|-------------------------|--------|-------------------------------------|
| Body weight <sup>a</sup> (kg)                               | 2.5                     | 70     | kg                                  |
| Tissue volumes (as fraction of body weight)                 |                         |        |                                     |
| Blood <sup>a,b</sup>                                        | 0.0734                  | 0.079  |                                     |
| Bone <sup>a,b</sup>                                         | 0.12                    | 0.12   |                                     |
| Brain <sup>a,b</sup>                                        | 0.036                   | 0.02   |                                     |
| Cerebellum <sup>a</sup>                                     | 0.08                    | 0.08   |                                     |
| Olfactory bulb <sup>a</sup>                                 | 0.0006                  | 0.0006 |                                     |
| Globus Pallidus <sup>a</sup>                                | 0.0015                  | 0.0015 |                                     |
| Pituitary <sup>a</sup>                                      | 0.0013                  | 0.0013 |                                     |
| Liver <sup>a,b</sup>                                        | 0.027                   | 0.026  |                                     |
| Lung <sup>a,b</sup>                                         | 0.008                   | 0.008  |                                     |
| Remaining body                                              | Difference <sup>g</sup> |        |                                     |
| Surface area of nasal respiratory epithelium <sup>c,d</sup> | 15.6                    | 9.81   | cm <sup>2</sup> /kg <sup>0.75</sup> |
| Surface area of nasal olfactory epithelium <sup>c,d</sup>   | 1.6                     | 0.52   | cm <sup>2</sup> /kg <sup>0.75</sup> |
| Average nasal tissue thickness <sup>e</sup>                 | 375                     | 375    | μm                                  |
| Cardiac output <sup>a,b</sup>                               | 19.5                    | 13.0   | l/h/kg                              |
| Pulmonary ventilation <sup>a,b</sup>                        | 30.0                    | 18.0   | l/h/kg                              |
| Tissue blood flow (as fraction of cardiac output)           |                         |        |                                     |
| Bone <sup>a,b</sup>                                         | 0.042                   | 0.042  |                                     |
| Brain <sup>a,b</sup>                                        | 0.065                   | 0.114  |                                     |
| Liver <sup>a,b</sup>                                        | 0.194                   | 0.227  |                                     |
| Nose <sup>f</sup>                                           | 0.01                    | 0.01   |                                     |
| Remaining body                                              | Difference <sup>g</sup> |        |                                     |

<sup>a</sup>Monkey values are from Davies and Morris (1993) or Dorman *et al.* (2006a).

<sup>b</sup>Human values are from Brown *et al.* (1997).

<sup>c</sup>Monkey values are from Menache *et al.* (1997).

<sup>d</sup>Human values are from Schroeter *et al.* (2008).

<sup>e</sup>Values are from Conolly *et al.* (2000).

<sup>f</sup>From Frederick *et al.* (1998).

<sup>g</sup>Difference = 1.0 – (sum of listed compartment).

into respiratory and olfactory deposition according to an airflow allocation of 9% olfactory and 91% respiratory (Kepler *et al.*, 1998).

Dissociation rate constants ( $k_a$  and  $k_d$ ), tissue binding capacities ( $B_{max}$ ), and diffusion parameters ( $k_{in}$  and  $k_{out}$ ) in each tissue compartment were calibrated to the pharmacokinetic data from Dorman *et al.* (2006a). In that study, monkeys were exposed by inhalation to MnSO<sub>4</sub> exposure atmospheres for 90 days (6 h/day, 5 days/week) at concentrations of 0, 0.06, 0.3, or 1.5 mg Mn/m<sup>3</sup>. Tissues were collected on the day following the last Mn exposure to determine tissue Mn concentrations. Dissociation rate constants and maximal binding capacities were adjusted so that each brain region contained approximately 60% bound Mn under dietary exposure only (i.e., with no inhalation). These parameters reflect a change in bound Mn fraction from that reported by Nong *et al.* (2009) (approximately 20% bound Mn) to provide a more consistent description of Mn binding in brain regions across animal species. Diffusion parameters were then adjusted to simulate the rise in brain Mn tissue levels following the onset of inhalation exposure and the subsequent decrease in Mn brain tissue concentrations following the end-of-the exposure period. Further refinements to brain kinetics in the globus pallidus and pituitary regions were included by adding the dose-dependent influx term so that simulations accurately predicted the rise in Mn tissue levels in these regions. Tissue binding and diffusion parameters are listed in Table 4.

**Human model parameterization.** Physiological parameters in the human PBPK model were either scaled from the monkey or were obtained from the literature (Brown *et al.*, 1997) (Table 1). An average body weight of 70 kg was used in all simulations. Human basal Mn tissue levels were obtained from

TABLE 2

## Basal Tissue Mn Concentrations in Monkeys and Humans

| Tissue          | Mn concentration<br>(μg Mn/g<br>tissue wet weight) |       |                                                                                                               |
|-----------------|----------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------|
|                 | Monkey <sup>a</sup>                                | Human | References for human values                                                                                   |
| Liver           | 2.49                                               | 1.2   | Sumino <i>et al.</i> (1975)                                                                                   |
| Lung            | 0.15                                               | 0.22  | Sumino <i>et al.</i> (1975)                                                                                   |
| Bone            | 0.08                                               | 0.074 | Sumino <i>et al.</i> (1975)                                                                                   |
| Blood           | 0.01                                               | 0.064 | Sumino <i>et al.</i> (1975)                                                                                   |
| Cerebellum      | 0.44                                               | 0.33  | Aschner <i>et al.</i> (2005) and<br>Bush <i>et al.</i> (1995) <sup>b</sup>                                    |
| Globus pallidus | 0.48                                               | 0.39  | Aschner <i>et al.</i> (2005),<br>Bush <i>et al.</i> (1995) <sup>b</sup> , and<br>Tracqui <i>et al.</i> (1995) |
| Olfactory bulb  | 0.31                                               | 0.67  | Bonilla <i>et al.</i> (1982) <sup>b</sup>                                                                     |
| Pituitary       | 0.84                                               | 0.46  | Thorlacius-Ussing <i>et al.</i> (1988) <sup>b</sup>                                                           |

<sup>a</sup>From Dorman *et al.* (2006a).

<sup>b</sup>Mn tissue concentrations in these references were reported as micrograms of Mn per gram dry tissue weight and were reduced by 80% to convert to wet tissue weight (Molokhia, 1967).

autopsy reports (Table 2). Dietary intake was set at 3 mg/day Mn, a value slightly higher than the adequate intake level (Aschner and Aschner, 2005). Dietary absorption (Fdiutp) and biliary excretion (kbilec) were calibrated to whole-body elimination kinetics from iv tracer doses of <sup>54</sup>Mn (Table 3) (Mahoney and Small, 1968; Mena *et al.*, 1967).

Human respiratory tract deposition of MnSO<sub>4</sub> particles was estimated with MPPD using standard ventilatory parameters for resting nasal breathing in adults: 12 breaths per minute and a tidal volume of 625 ml. Nasal and lung deposition were estimated to be 37.6 and 25%, respectively. Deposition on human olfactory epithelium was assumed to be 5% of total nasal deposition based on olfactory airflow allocation (Schroeter *et al.*, 2010).

Interspecies scaling from monkeys to humans was based on allometric scaling for flows (BW<sup>0.75</sup>) and volumes body weight (BW). For the initial human model parameterization, diffusion rate constants for brain compartments

TABLE 3

## Dietary Absorption and Biliary Elimination Parameters in Monkeys and Humans

| Parameter         | Description                                          | Monkey              | Human               | Units  |
|-------------------|------------------------------------------------------|---------------------|---------------------|--------|
| Fdiutp            | Fractional gut absorption                            | 0.0021 <sup>a</sup> | 0.06 <sup>b</sup>   |        |
| kbilec            | Biliary excretion rate constant <sup>c</sup>         | 0.051               | 0.051               | l/h/kg |
| k <sub>bmax</sub> | Maximal biliary excretion rate constant <sup>d</sup> | 2.5                 | 2.5                 | l/h    |
| k <sub>b50</sub>  | Affinity rate constant <sup>d</sup>                  | 0.027               | 0.027               | μg/ml  |
| n                 | Slope factor <sup>d</sup>                            | 3                   | 3                   |        |
| k <sub>GI</sub>   | Transfer rate from gut lumen                         | 0.6 <sup>e</sup>    | 0.026 <sup>f</sup>  | /h     |
| F <sub>ENT</sub>  | Fractional enterocyte storage                        | 0.011 <sup>e</sup>  | 0.005 <sup>f</sup>  |        |
| k <sub>ENT</sub>  | Enterocyte sloughing rate                            | 0.0022 <sup>e</sup> | 0.0022 <sup>f</sup> | /h     |

<sup>a</sup>Calibrated with a 133-ppm Mn diet to the data from Dorman *et al.* (2006a).

<sup>b</sup>Calibrated using a 3 mg/day Mn diet to the data from Mahoney and Small (1968) and Mena *et al.* (1967).

<sup>c</sup>kbile is allometrically scaled (kbile = kbilec × BW<sup>0.75</sup>).

<sup>d</sup>see Equation 1.

<sup>e</sup>Calibrated to the data from Furchner *et al.* (1966).

<sup>f</sup>Calibrated to the data from Davidsson *et al.* (1988).

were scaled from the monkey as  $BW^{-0.25}$  because they represent clearance terms divided by tissue volume. Tissue binding capacity ( $B_{\max}$ ) was scaled by tissue volume. Association and dissociation rate constants ( $k_a$  and  $k_d$ ) were modified from monkey values to yield a higher bound fraction in human brain regions (80% bound Mn under dietary exposure only) compared with that in monkeys. This reflects the greater bound Mn storage requirements associated with lower Mn dietary intake in humans. Inhalation exposure simulations were also conducted assuming a 60% bound Mn fraction in humans to test the sensitivity of this assumption. Since there are further physiological and biochemical differences between monkeys and humans that affect Mn uptake and storage, a direct scaling of parameters between species did not adequately describe steady-state Mn tissue levels. Although parameters were retained across species to the extent possible, additional refinements to model parameters were employed to maintain basal tissue levels with only dietary Mn exposure (i.e., no inhalation). The final dissociation rate constants, maximal binding capacities, and diffusion parameters for the human model are listed in Table 4.

**Inhalation exposure simulations.** Mn inhalation exposure was simulated in monkeys for 90 days (6 h/day, 5 days/week) to be consistent with the study by Dorman *et al.* (2006a). Mn inhalation exposures in humans were simulated for 90 days (8 h/day, 5 days/week), unless otherwise noted.

## RESULTS

### <sup>54</sup>Mn Tracer Kinetics in Monkeys

The Mn PBPK model simulated <sup>54</sup>Mn tracer kinetics in monkeys exposed by ip, iv, and sc injection and by oral and

inhalation routes. Exposure routes were selected based on whole-body elimination or fecal excretion data available from <sup>54</sup>Mn tracer kinetic studies in monkeys. Fractional dietary absorption (Fdietup) and biliary excretion (kbilec) were adjusted for each exposure scenario to account for the different Mn diets and body weights used in each study (Table 5). These parameters were calibrated to maintain the basal tissue Mn levels reported by Dorman *et al.* (2006a) prior to exposure and to fit whole-body retention or fecal excretion data of <sup>54</sup>Mn. All the other parameters in the PBPK model were unchanged to maintain a consistent description of Mn tissue kinetics regardless of exposure route.

In the study by Dastur *et al.* (1971), 12 rhesus monkeys with an average body weight of 2.5 kg were administered an ip dose of 200  $\mu$ Ci of carrier-free <sup>54</sup>MnCl<sub>2</sub> solution. Whole-body activity of <sup>54</sup>Mn was reported up to 278 days postexposure. The amount of Mn in the diet was not stated, so an 80-ppm Mn diet was used to be consistent with other published studies (Furchner *et al.*, 1966). Because this was lower than the 133-ppm Mn diet used by Dorman *et al.* (2006a) for model calibration, Fdietup was increased to 0.00345 to calibrate steady-state tissue Mn levels. Rapid elimination of <sup>54</sup>Mn from the body was observed in the first 50 days following ip injection. This phase was followed by a slow phase of

**TABLE 4**  
Tissue Mn Binding Capacity and Diffusion Parameters for Monkeys and Humans

|                           | Binding                        |                     |            | Diffusion        |                   |             |                       |
|---------------------------|--------------------------------|---------------------|------------|------------------|-------------------|-------------|-----------------------|
|                           | $B_{\max}$ ( $\mu$ g/g tissue) | $k_a$ (/ $\mu$ g/h) | $k_d$ (/h) | $k_{in}$ (/h/kg) | $k_{out}$ (/h/kg) | $k_{inmax}$ | $k_{in50}$ ( $\mu$ g) |
| <b>Monkey<sup>a</sup></b> |                                |                     |            |                  |                   |             |                       |
| <b>Brain</b>              |                                |                     |            |                  |                   |             |                       |
| Cerebellum                | 550                            | 0.001               | 0.0014     | 4.3              | 0.08              |             |                       |
| Olfactory                 | 700                            | 0.3                 | 0.005      | 2.9              | 11.0              |             |                       |
| <b>bulb</b>               |                                |                     |            |                  |                   |             |                       |
| Globus                    | 600                            | 0.2                 | 0.0056     | 0.16             | 0.3               | 7.9         | 0.16                  |
| <b>pallidus</b>           |                                |                     |            |                  |                   |             |                       |
| Pituitary                 | 2000                           | 0.3                 | 0.036      | 0.129            | 0.2               | 10.0        | 0.2                   |
| Liver                     | 4000                           | 0.0011              | 0.0004     |                  |                   |             |                       |
| Lung                      | 2700                           | 0.01                | 0.038      |                  |                   |             |                       |
| Bone                      | 600                            | 0.00464             | 0.024      |                  |                   |             |                       |
| Remaining body            | 200                            | 0.0093              | 0.0045     |                  |                   |             |                       |
| <b>Human<sup>b</sup></b>  |                                |                     |            |                  |                   |             |                       |
| <b>Brain</b>              |                                |                     |            |                  |                   |             |                       |
| Cerebellum                | 370                            | 0.001               | 0.003      | 2.4              | 0.08              |             |                       |
| Olfactory                 | 620                            | 0.35                | 0.005      | 3.0              | 7.5               |             |                       |
| <b>bulb</b>               |                                |                     |            |                  |                   |             |                       |
| Globus                    | 500                            | 0.2                 | 0.02       | 0.08             | 0.4               | 4.6         | 0.16                  |
| <b>pallidus</b>           |                                |                     |            |                  |                   |             |                       |
| Pituitary                 | 620                            | 0.3                 | 0.036      | 0.079            | 0.3               | 3.5         | 0.2                   |
| Liver                     | 1245                           | 0.0011              | 0.00048    |                  |                   |             |                       |
| Lung                      | 460                            | 0.01                | 0.038      |                  |                   |             |                       |
| Bone                      | 78                             | 0.00464             | 0.024      |                  |                   |             |                       |
| Remaining body            | 84                             | 0.0093              | 0.0045     |                  |                   |             |                       |

<sup>a</sup>Kinetic parameters for the monkey model were calibrated to the pharmacokinetic data from Dorman *et al.* (2006a).

<sup>b</sup>Kinetic parameters for the human model were adjusted from the monkey parameters to maintain the basal tissue levels in Table 2 with no Mn inhalation.

elimination for the remaining time. The parameters  $F_{IP} = 0.03$  and  $k_{IP} = 1.0 \times 10^{-7}/h$  were calibrated to the whole-body elimination data to simulate the slow release of  $^{54}\text{Mn}$  from the peritoneal cavity to the liver. With these adjustments to specific parameters, model simulations were consistent with the nonlinear kinetics of  $^{54}\text{Mn}$  observed by ip administration (Fig. 2A).

In the study by Furchner *et al.* (1966), 0.6  $\mu\text{Ci}$  of carrier-free  $^{54}\text{MnCl}_2$  was administered iv to three rhesus monkeys with an average body weight of 8.5 kg. The monkeys were maintained on a commercial diet containing 80 ppm Mn. Whole-body  $^{54}\text{Mn}$  activity was measured for 290 days. Fdietup was reduced to 0.0017 to account for the higher levels of Mn ingested by the larger monkeys and to maintain stable background Mn tissue levels. After 300 days, whole-body retention after ip and iv administration were very similar, but initial clearance was much faster after ip dosing (Figs. 2A and 2B).

Furchner *et al.* (1966) also orally dosed three rhesus monkeys with 0.6  $\mu\text{Ci}$  of carrier-free  $^{54}\text{MnCl}_2$ . These monkeys had an average body weight of 7 kg and were also maintained on an 80-ppm Mn commercial diet. Whole-body activity of  $^{54}\text{Mn}$  was measured for 23 days postexposure. Parameters governing GI absorption ( $k_{GI}$ ,  $F_{ENT}$ , and  $k_{ENT}$ ) were calibrated based on the oral  $^{54}\text{Mn}$  tracer data. Fdietup was set to 0.002 to maintain consistent background Mn tissue levels. Rapid elimination of  $^{54}\text{Mn}$  was observed in the first 5 days following oral administration of Mn that was not taken up systemically followed by a slow elimination phase for the remaining time period (Fig. 2C).

In the study by Newland *et al.* (1987), one monkey (*Macaca nemistrina*, 5 kg) received a 6-week continuous infusion of  $^{54}\text{Mn}$  through two sc osmotic pumps implanted between the shoulder blades. Each solution contained 200  $\mu\text{Ci}$   $^{54}\text{Mn}$  and 400 mg Mn in an  $\text{MnCl}_2$  solution. As noted by the authors, there was leakage at the osmotic pump implant sites, so the reported doses represent an estimate of the maximum dose as calculated from the pumping rate, and the actual dose received by the monkey could have been lower. For PBPK model simulations, the maximal dose as reported by Newland *et al.* (1987) was used. Fecal  $^{54}\text{Mn}$  activity was measured for approximately 160 days. Fecal  $^{54}\text{Mn}$  concentrations were elevated during the exposure period and were relatively constant. A rapid decrease in fecal  $^{54}\text{Mn}$  concentration was observed immediately following removal of the sc pumps (Fig. 3A). This rapid elimination phase was followed by a slow elimination phase for the remaining observation period. Rapid clearance of  $^{54}\text{Mn}$  following sc exposure appears to be because of dose rate differences and not to the route of administration. Because the osmotic pump solution contained a high concentration of carrier (400 mg of Mn), the kinetics are not equivalent to carrier-free radiotracer kinetics.

Newland *et al.* (1987) exposed two anesthetized monkeys (*Macaca fascicularis*, 2.5 and 3.1 kg) to a nebulized aerosol of  $^{54}\text{MnCl}_2$  for 30 min through a tracheal tube. Each monkey was

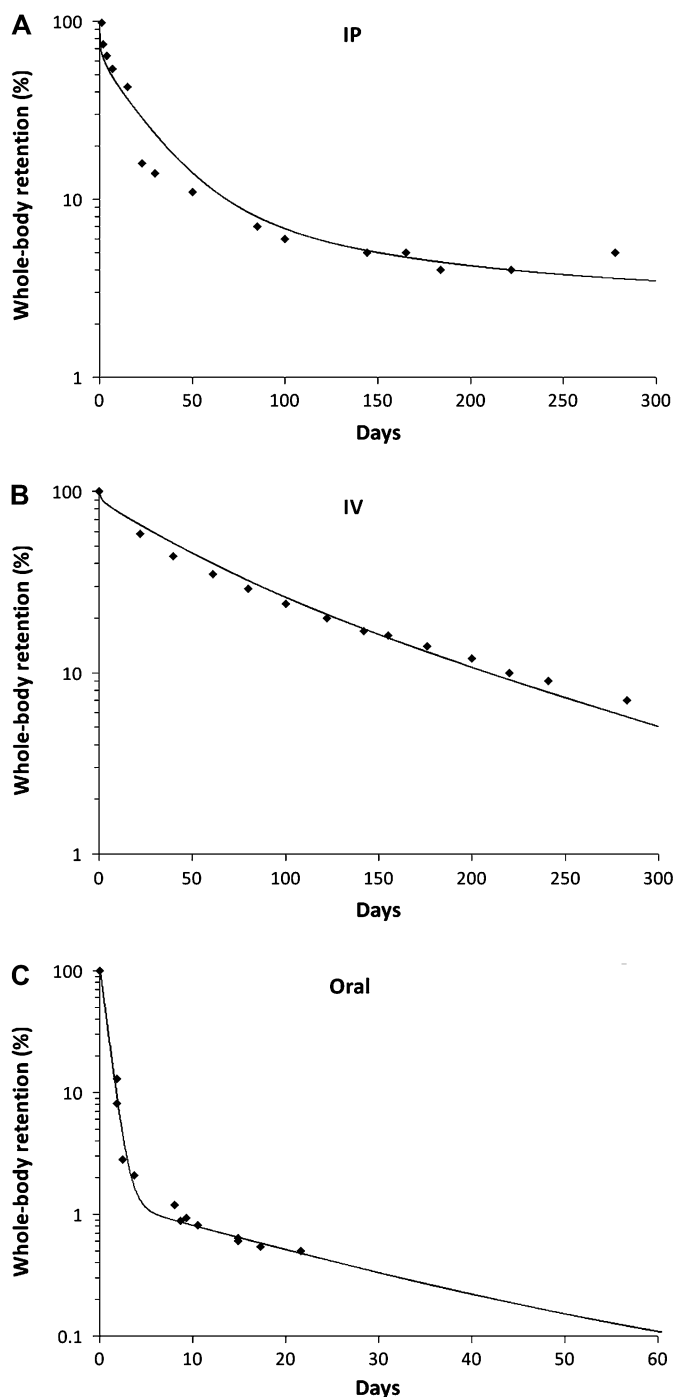


**FIG. 2.** Simulated whole-body retention of  $^{54}\text{Mn}$  in monkeys compared with experimental data using different exposure routes: (A) monkeys were exposed by ip injection to 200  $\mu\text{Ci}$   $^{54}\text{MnCl}_2$  (Dastur *et al.*, 1971); Fdietup = 0.00345, kbilec = 0.051; (B) monkeys were exposed by iv administration to 0.6  $\mu\text{Ci}$   $^{54}\text{MnCl}_2$  (Furchner *et al.*, 1966); Fdietup = 0.0017, kbilec = 0.051; (C) monkeys were orally dosed with 0.6  $\mu\text{Ci}$  of  $^{54}\text{MnCl}_2$  (Furchner *et al.*, 1966); Fdietup = 0.002, kbilec = 0.051. The curves represent model simulations and the symbols are retention data from individual monkeys.

exposed to a different aerosol with different specific activities. Fecal gamma activity was reported for approximately 250 days. The lung dose for each aerosol was estimated to be 16% by Newland *et al.* (1987). Calibrated dietary parameters in the PBPK model were  $F_{dietup} = 0.001$  and  $kbilec = 0.015$  to fit background Mn tissue levels and obtain fecal elimination rates consistent with the data. Fecal Mn declined rapidly in the first few days following exposure, followed by a slow decline for the remaining time period (Fig. 3B).

#### <sup>54</sup>Mn Tracer Kinetics in Humans

<sup>54</sup>Mn tracer kinetics were also available for humans given an iv dose of <sup>54</sup>MnCl<sub>2</sub>. In the study by Mahoney and Small (1968), three normal subjects (identified in Fig. 4 by their initials: HM, MM, and CH) were given an iv dose of 2.5  $\mu$ Ci of <sup>54</sup>Mn. Whole-body retention of <sup>54</sup>Mn was measured for 60 days. No information was given in the study regarding the subjects' gender, body weight, or diet. In another study by

Mena *et al.* (1967), eight healthy medical personnel were injected with an iv dose of 20  $\mu$ Ci <sup>54</sup>Mn, and whole-body retention was measured for 30 days. Observations of whole-body clearance of <sup>54</sup>Mn from both studies were consistent (Fig. 4), with all subjects showing a gradual decrease in <sup>54</sup>Mn retention from near 100% at day 1 to about 40% on day 30. Additionally, whole-body retention in the three subjects in the study of Mahoney and Small (1968) decreased to 20–30% by day 60. Clearance curves revealed a fast elimination component in the first few days followed by a slow elimination component for the remaining time period, consistent with <sup>54</sup>Mn clearance observations in nonhuman primates and other species. Dietary absorption and biliary excretion rate constants in the human model were calibrated to the whole-body retention data from these two studies. The biliary excretion rate constant ( $kbilec = 0.051$ ) and biliary induction parameters were identical to those used for the monkey. Fractional dietary absorption was higher in humans ( $F_{dietup} = 0.06$ ) than in monkeys because of the lower amount of Mn in the human diet. Model simulations recapitulated the decrease in human whole-body retention of <sup>54</sup>Mn observed over the 60-day time frame (Fig. 4).

To study dose-dependent effects of Mn intake on <sup>54</sup>Mn clearance rates, Mahoney and Small (1968) also analyzed whole-body retention of <sup>54</sup>Mn in subjects receiving supplemental Mn. One subject (subject JM) was on a voluntary reduced calorie diet (800 calories per day) for 6 months prior to the start of the study. This subject was given an iv dose of 2.5  $\mu$ Ci of <sup>54</sup>Mn at the start of the study, and whole-body retention was measured periodically. The reduced calorie diet was continued throughout the observation period. Sixty days after the <sup>54</sup>Mn injection, the subject began to ingest 800 mg/day of

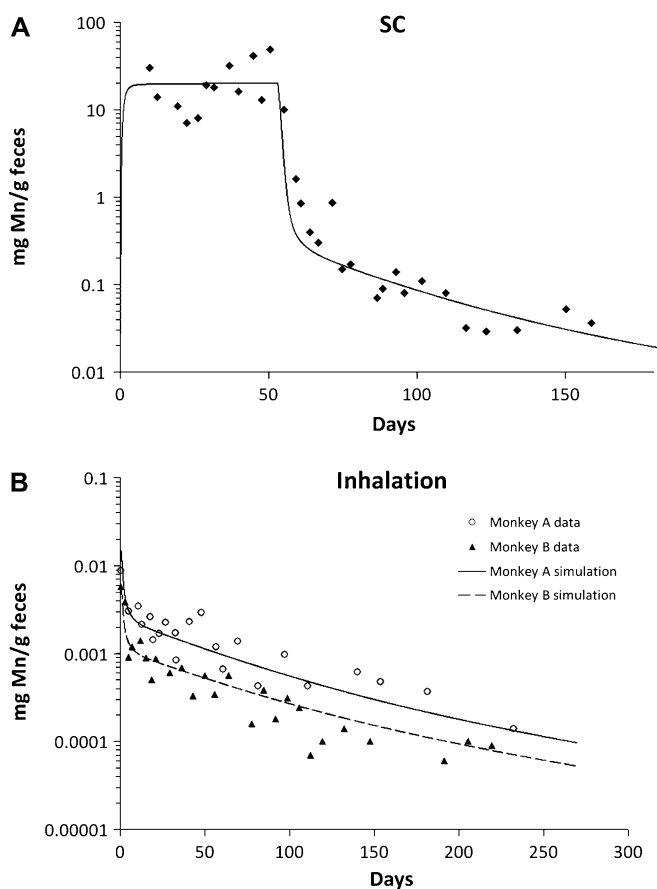


**FIG. 3.** Simulated fecal excretion of <sup>54</sup>Mn in monkeys compared with the experimental data from Newland *et al.* (1987): (A) one monkey was injected sc with 200  $\mu$ Ci <sup>54</sup>Mn and 400 mg Mn in an MnCl<sub>2</sub> solution;  $F_{dietup} = 0.0025$ ,  $kbilec = 0.051$ ; (B) two monkeys were exposed by inhalation to a nebulized aerosol of <sup>54</sup>MnCl<sub>2</sub>;  $F_{dietup} = 0.001$ ,  $kbilec = 0.015$ . The curves represent model simulations and the symbols are fecal excretion data from individual monkeys.

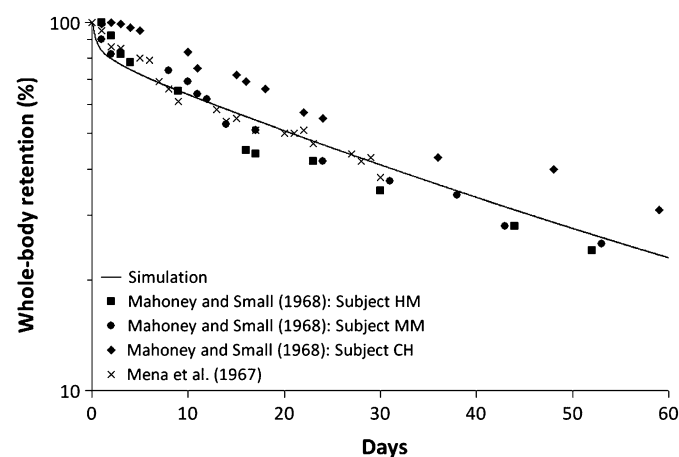


**FIG. 4.** Comparison of simulated whole-body retention in humans given an iv dose of <sup>54</sup>Mn with the whole-body retention data of Mahoney and Small (1968) and Mena *et al.* (1967). The curve represents the model simulation; the symbols for the study of Mahoney and Small (1968) are retention data for individual subjects; and the symbols for the study of Mena *et al.* (1967) represent average retention from eight subjects.  $F_{dietup} = 0.06$ ,  $kbilec = 0.051$ .

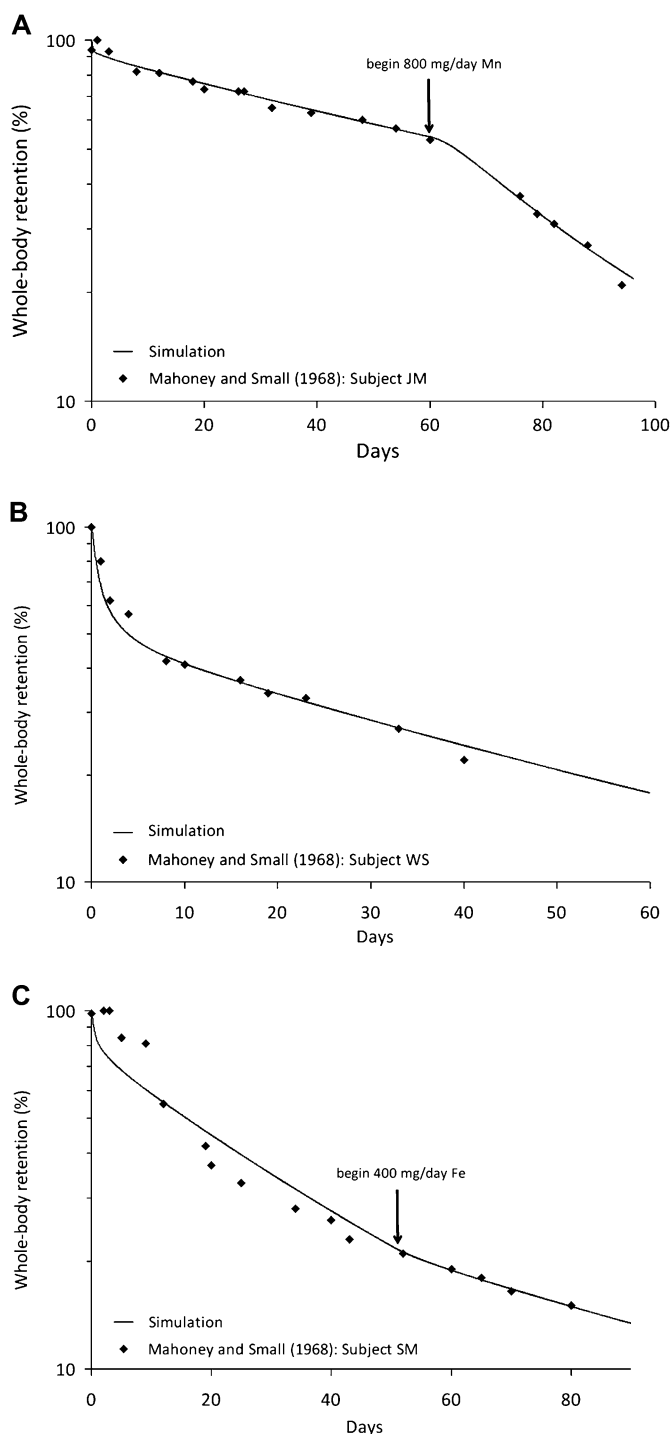


**FIG. 5.** Comparison of simulated whole-body retention of  $^{54}\text{Mn}$  in human volunteers given supplemental Mn or Fe compared with the experimental data from Mahoney and Small (1968): (A) subject JM was on a reduced calorie diet and began to ingest 800 mg/day Mn on day 60 of the study; (B) subject WS was preloaded with 300 mg/day Mn 10 days prior to the start of the study; (C) subject SM had an iron deficiency and began to ingest 400 mg/day Fe on day 50. The condition of each subject was accommodated in the PBPK model by adjusting Mn dietary absorption (Fdietup). The curves represent model simulations and the symbols are retention data from individual subjects.

Mn as an  $\text{MnCl}_2$  solution. Whole-body retention measurements of  $^{54}\text{Mn}$  continued for another 25 days to examine the effect of the “flushing dose” of ingested Mn on  $^{54}\text{Mn}$  clearance (Fig. 5A). Before the high Mn dose was ingested, whole-body retention was higher in the reduced calorie subject than in the normal subjects because of decreased biliary elimination from the presumably lower Mn in the calorie-restricted diet. At day 30, retention in the subject on the reduced calorie diet was about 65% compared with about 40% in normal subjects. After the high Mn ingestion period began, a rapid increase in  $^{54}\text{Mn}$  clearance was observed. For the PBPK model simulations, the reduced calorie diet was simulated by assuming 1 mg Mn/day in the diet. As a result of the reduced calorie diet, Mn dietary absorption increased. Fdietup was increased slightly to 0.062 to fit the whole-body retention data until day 60. Once the flushing Mn dose was ingested, Fdietup was reduced to 0.00046 to account for decreased GI absorption of these high Mn oral doses. With these changes in dietary absorption corresponding to the different amounts of Mn ingested, the PBPK model simulations were consistent with  $^{54}\text{Mn}$  whole-body retention data for this subject (Fig. 5A).

To examine another high-dose Mn scenario, another subject (subject WS) in the study of Mahoney and Small (1968) that was on a normal diet was preloaded for 10 days prior to iv injection of  $^{54}\text{Mn}$  by ingesting 300 mg Mn/day as an  $\text{MnCl}_2$  solution. This dosing schedule continued throughout the experiment for an additional 40 days. The disappearance of  $^{54}\text{Mn}$  from the body was much more rapid in the subject preloaded with Mn than in normal subjects (Fig. 5B). Ten days after the  $^{54}\text{Mn}$  iv injection, approximately 40% remained in the body compared with about 70% in normal subjects. For the model simulations, Mn dietary absorption was reduced by 28% per day for 15 days beginning at the start of the high-dose Mn ingestion. After 15 days, Fdietup was then kept constant at its reduced value of 0.00043 for the remainder of the exposure period. This adjustment accounts for the slow decrease in dietary absorption of Mn from moderately high doses over extended time periods (Fig. 5B).

Mahoney and Small (1968) also investigated  $^{54}\text{Mn}$  retention in a mildly iron-deficient subject and found that  $^{54}\text{Mn}$  clearance was faster in the iron-deficient subject than in normal subjects (Fig. 5C). Fifty days after  $^{54}\text{Mn}$  administration, iron therapy was initiated with 400 mg/day Fe. This immediately decreased the elimination rate of  $^{54}\text{Mn}$  from the body. Model simulations recapitulated whole-body retention in this subject by increasing Mn absorption (Fdietup = 0.075) during the iron-deficient phase and decreasing Mn absorption (Fdietup = 0.035) after the initiation of iron therapy (Fig. 5C). This behavior was consistent with previous findings where decreased Mn absorption was observed with high iron intake (Davis *et al.*, 1992; Finley, 1999). The interaction of Mn and Fe absorption is likely because of the fact that both metals share common uptake and storage transporters such as divalent metal transporter-1 and transferrin, so increases in the dietary



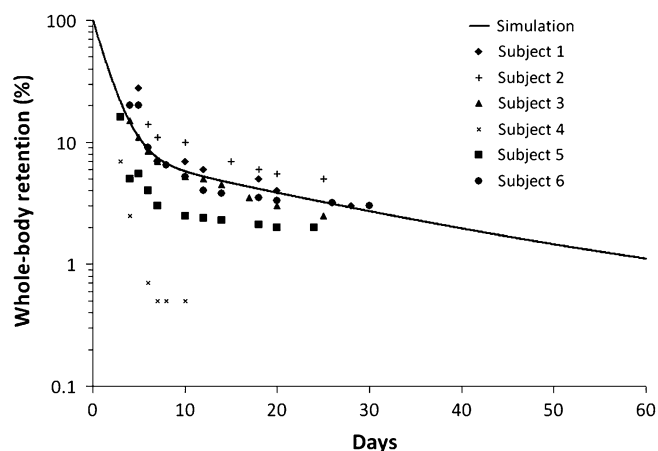


**FIG. 6.** Comparison of simulated whole-body retention of  $^{54}\text{Mn}$  in humans with the experimental data from Davidsson *et al.* (1988), where female volunteers ingested a meal labeled with  $^{54}\text{Mn}$ . The curve represents a model simulation and the data symbols are from individual subjects.  $\text{Fdietup} = 0.12$ ,  $\text{kbilec} = 0.102$ .

concentration of one element inhibit absorption and transport of the other (Fitsanakis *et al.*, 2010).

Oral Mn exposures were used to calibrate GI parameters in the PBPK model (Table 4). In the study by Davidsson *et al.* (1988), whole-body retention of  $^{54}\text{Mn}$  was measured in six women who ingested a meal labeled with 0.1 MBq  $^{54}\text{Mn}$  (Fig. 6). A wide range of elimination rates was observed in the subjects, but all showed rapid elimination in the first 10 days followed by a slow phase of elimination for the remaining period (Fig. 6). The shape of the retention curve was similar to that observed in monkeys receiving an oral dose of  $^{54}\text{MnCl}_2$  (Fig. 2).  $\text{Fdietup}$  and  $\text{kbilec}$  were increased twofold for this simulation to account for increased Mn dietary absorption and biliary excretion in women (Aschner and Aschner, 2005). Simulated plasma Mn concentrations were also compared with plasma Mn measurements from men consuming different levels of dietary Mn (Freeland-Graves, 1994). Although the model predicted larger differences in plasma Mn concentration at the lowest and highest dietary levels, model simulations accurately captured the trend of plasma Mn levels caused by changes in dietary Mn exposure (Fig. 7).

#### Mn Inhalation Exposures in Monkeys and Humans

Basal tissue Mn levels were set to the measurements reported by Dorman *et al.* (2006a) for control monkeys on a 133-ppm Mn diet by adjusting dietary absorption and biliary excretion (Table 4). The monkey PBPK model parameters were first scaled from the rat values and were further calibrated to the pharmacokinetic data in Dorman *et al.* (2006a). Predicted brain tissue concentrations in monkeys were then compared with Mn concentrations observed in monkeys exposed for a 90-day period (Dorman *et al.*, 2006a). At an exposure concentration of 1.5  $\text{mg}/\text{m}^3$  Mn, predicted Mn tissue concentrations in the four

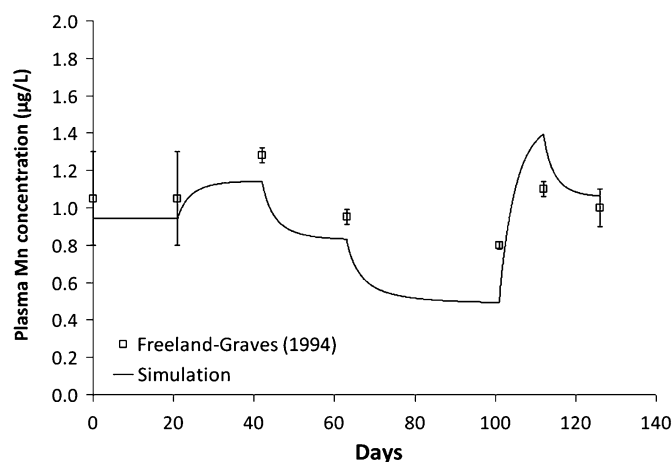


**FIG. 7.** Comparison of simulated plasma Mn concentrations with the experimental data from Freeland-Graves (1994). Simulated plasma Mn concentrations were calculated as 20% of simulated blood Mn concentrations. The data points represent the average plasma Mn concentration from five healthy men consuming diets containing different levels of dietary Mn (mean  $\pm$  SD)—Days 1–21: 2.36, Days 22–42: 2.89, Days 42–63: 2.06, Days 64–101: 1.21, Days 102–112: 3.79, Days 113–125: 2.65 mg Mn/day.  $\text{Fdietup} = 0.06$ ,  $\text{kbilec} = 0.051$ .

brain regions (globus pallidus, pituitary, cerebellum, and olfactory bulb) were consistent with the rapid rise in tissue concentrations after the onset of high inhalation exposure followed by the decline to near basal levels in the 90 days following cessation of exposure (Fig. 8). Predicted time-dependent Mn tissue concentrations were also consistent with the rise in end-of-exposure brain tissue levels at different inhaled concentrations (Fig. 9). Predicted Mn tissue concentrations were similar to those reported by Nong *et al.* (2009) except that wider fluctuations in brain Mn concentrations during inhalation were observed because of the increase in magnitude of the diffusional rate constants.

In the human model, dietary absorption and biliary elimination were calibrated to  $^{54}\text{Mn}$  whole-body retention data, as described previously (Table 3). Dissociation rate constants, maximal tissue binding, and diffusion rate constants were first scaled from the monkey and were then adjusted to fit the basal Mn tissue levels under dietary exposure only, assuming a 3 mg/day Mn diet (Table 4). Differences in parameter values between monkeys and humans are because of different basal Mn tissue levels between species (Table 2). Predicted brain Mn concentrations in humans were obtained for an inhalation exposure period of 90 days (8 h/day, 5 days/week) to simulate an occupational exposure and to be consistent with the inhalation exposure period used in the monkey simulations for direct comparison between species. Like monkeys, human brain Mn concentrations during this simulated exposure period exhibited a rapid rise in Mn tissue levels following the onset of exposure (Fig. 10). This was followed by a slower decline in human Mn tissue levels following the end of the exposure period. Simulated Mn

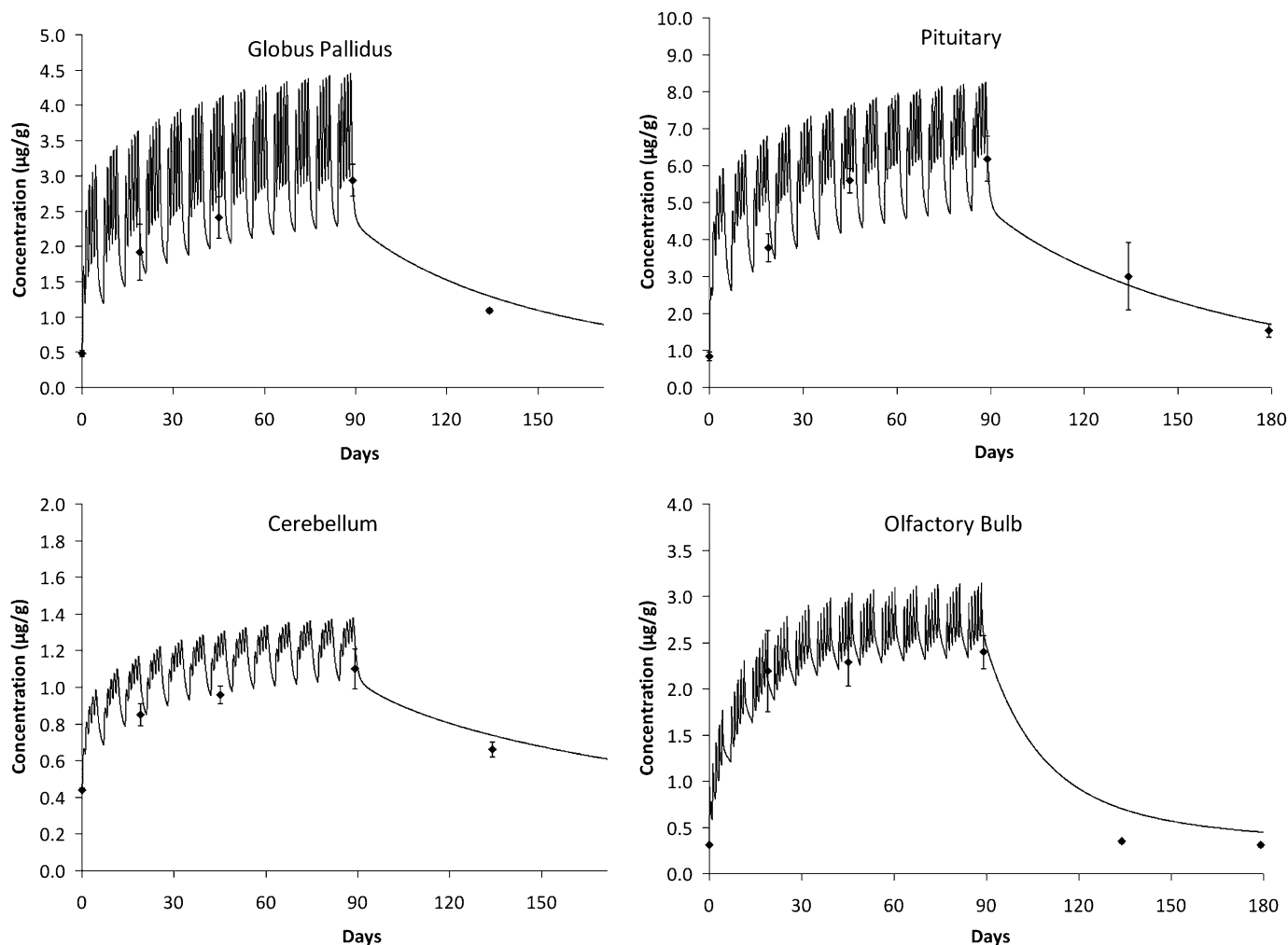


**FIG. 8.** Simulated brain tissue Mn levels in monkeys exposed by inhalation to  $1.5 \text{ mg Mn/m}^3$  for 90 days (6 h/day, 5 days/week). The simulation results are compared with data from Dorman *et al.* (2006a). The curves are model simulations and symbols are means and SEs from four to six monkeys per exposure concentration.

concentrations in the human globus pallidus were also examined during a 90-day exposure to Mn concentrations of  $0.01\text{--}5.0 \text{ mg/m}^3$  (Fig. 11). At the lowest exposure concentration ( $0.01 \text{ mg/m}^3$  Mn), the model predicted no appreciable increase ( $< 1\%$ ) in brain Mn concentrations above background levels that result from normal dietary exposure. At an exposure concentration of  $0.1 \text{ mg/m}^3$ , slight increases ( $\sim 5\%$ ) in brain Mn concentration above background levels were observed during the inhalation exposure period. More significant ( $> 30\%$ ) increases in brain Mn concentrations were predicted at the higher exposure concentrations ( $> 1.0 \text{ mg/m}^3$ ).

#### Sensitivity Analysis

Sensitivity coefficients for predicted globus pallidus concentration from a 1% change in model parameter values were determined at inhalation exposure concentrations of  $0.01$ ,  $0.1$ , and  $1.0 \text{ mg/m}^3$  Mn in monkeys and humans (Table 6). Model predictions were most sensitive to the influx and efflux

diffusion rate constants ( $k_{\text{in}}$  and  $k_{\text{out}}$ ). Model predictions were also sensitive to dietary absorption ( $F_{\text{dietup}}$ ) and biliary elimination ( $k_{\text{bilec}}$ ), although predictions became less sensitive with increasing exposure concentration as brain Mn levels were driven more by inhalation than diet. Sensitivity toward tissue-binding constants ( $B_{\text{max}}$ ,  $k_a$ , and  $k_d$ ) decreased as inhalation exposure concentration increased because of saturation of the tissue-binding capacity. Sensitivity of model predictions displayed similar trends in monkeys and humans and were consistent with sensitivity results in rats (Nong *et al.*, 2009). Sensitivity coefficients for other brain regions are presented in the Supplementary data

#### DISCUSSION

The PBPK model structure included commonly used exposure routes to take advantage of the multitude of  $^{54}\text{Mn}$

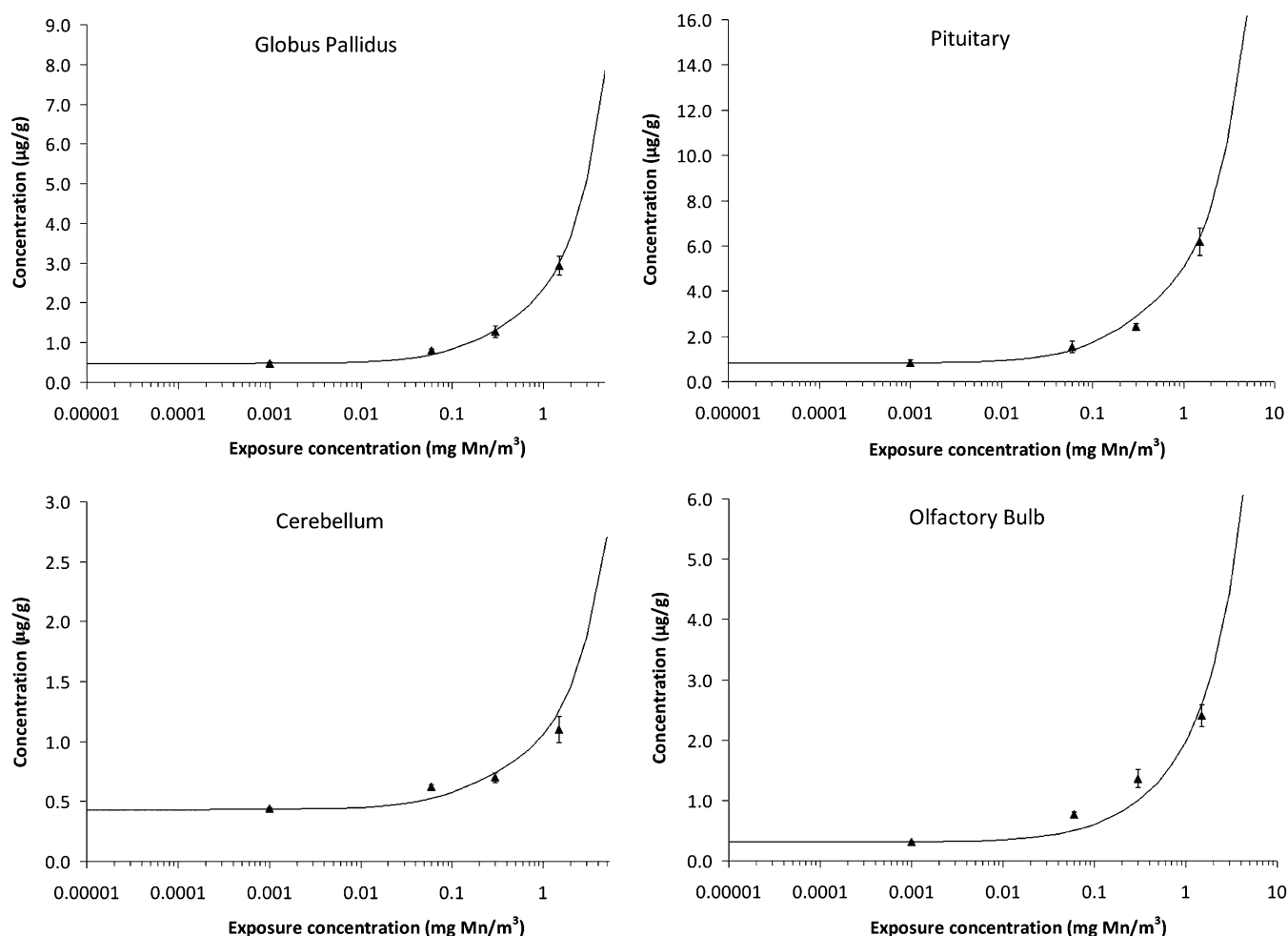


**FIG. 9.** Simulated end-of-exposure brain tissue Mn concentrations as a function of inhalation exposure concentration (milligrams of Mn per cubic meter). The simulation results are compared with data from Dorman *et al.* (2006a). Monkeys were exposed by inhalation for 90 days (6 h/day, 5 days/week). The curves are model simulations and symbols are means and SEs from four to six monkeys per exposure concentration.

clearance studies that have been conducted in monkeys and humans. A common feature from all these studies was that  $^{54}\text{Mn}$  clearance from the body follows biphasic elimination, with a short “fast” elimination phase (with halftimes of around a few days) followed by a longer “slow” elimination phase. This elimination behavior was consistently observed with all exposure routes. The availability of tracer studies for multiple exposure routes permitted a comparison of dose route differences in elimination. The fastest clearance in monkeys and humans occurred from oral exposure, whereas the slowest clearance occurred following iv administration. Oral clearance has a component related to limited GI uptake and passage of 95–99% of the oral dose through the GI tract into feces. The ability of the models to accurately replicate the elimination phases observed in these tracer studies provides confidence that the PBPK model structure accurately depicts the key aspects of Mn pharmacokinetics in monkeys and humans, irrespective of exposure route.

Cotzias and Greenough (1958) and Dorman *et al.* (2001b) showed that  $^{54}\text{Mn}$  clearance rates were affected by dietary Mn levels in mice and rats, respectively. Rats and mice given high Mn diets had significantly higher clearance rates when compared with animals kept on lower Mn diets. Similar findings were observed in humans by Mahoney and Small (1968), where a subject on a reduced calorie diet (which presumably resulted in lower Mn intake) had a much reduced elimination rate than subjects on a normal Mn diet. These effects arise from adaptive responses in Mn kinetics as oral doses vary. Model simulations reproduced the clearance rates of the individual on the reduced calorie diet by slightly increasing dietary absorption. The biliary excretion rate constant was reduced in the model simulations for this Mn-deficient individual because they also had decreased biliary elimination as evidenced by their reduced whole-body  $^{54}\text{Mn}$  clearance rates.

The elimination kinetics of the  $^{54}\text{Mn}$  tracer were influenced by the total administered Mn dose. Although elimination of

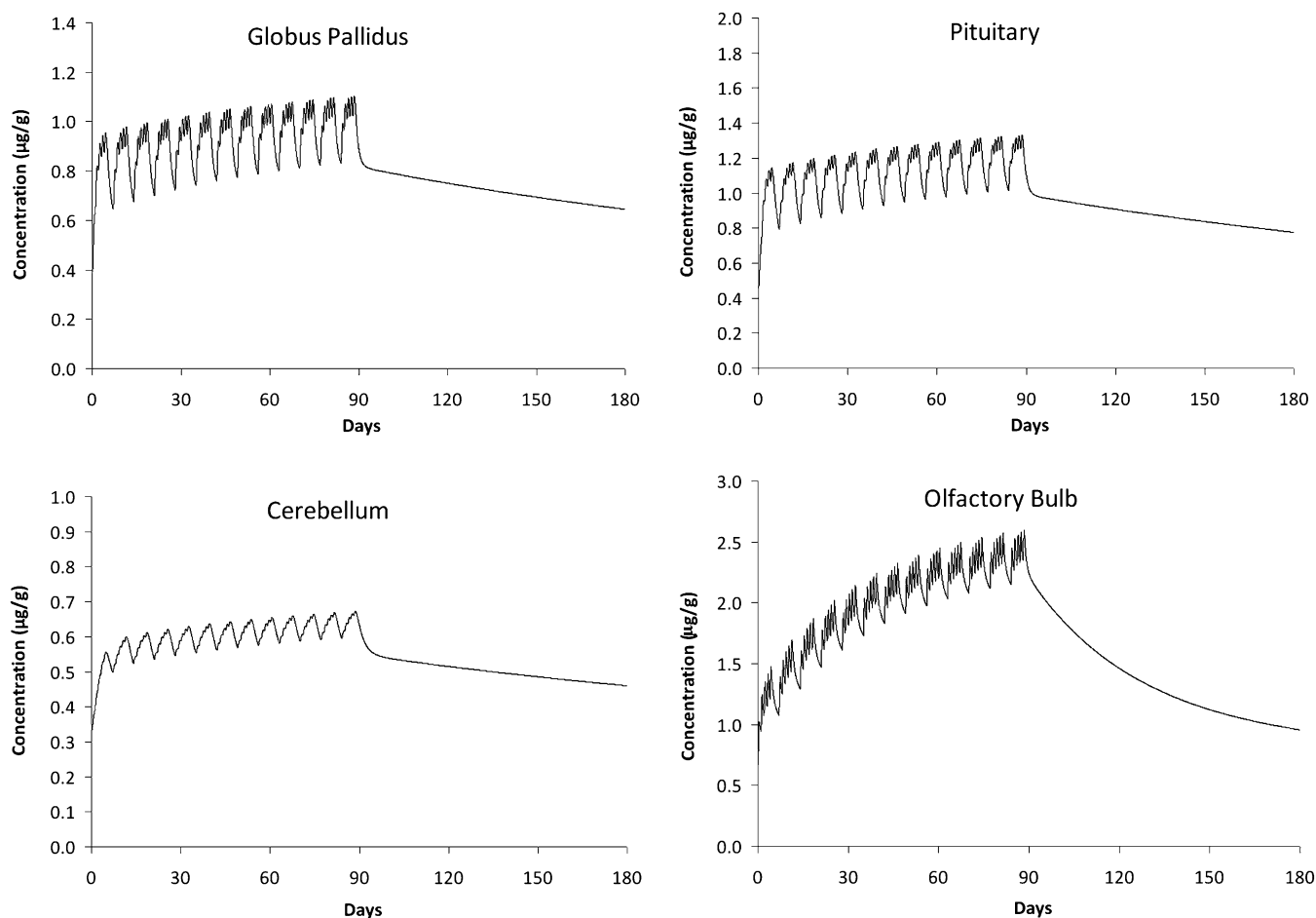


**FIG. 10.** Simulated brain tissue Mn levels in humans exposed by inhalation to 1.5 mg Mn/m<sup>3</sup> for 90 days (8 h/day, 5 days/week).

carrier-free <sup>54</sup>Mn exhibited similar behavior across dose routes and species, dose dependencies became more apparent when high levels of supplemental (carrier) Mn were added. In the

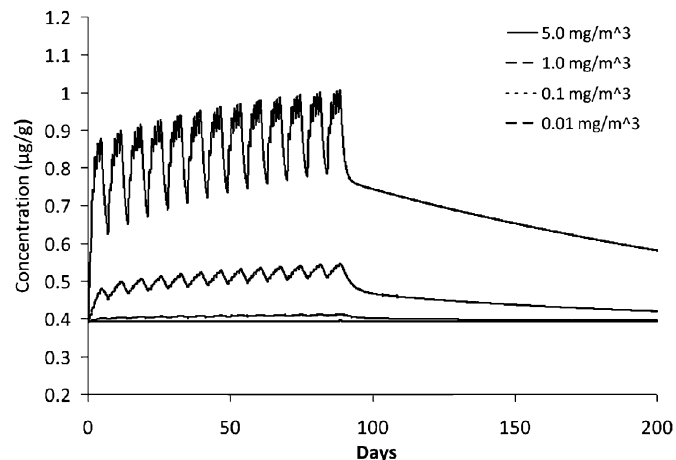


**FIG. 11.** Simulated human globus pallidus Mn concentrations during a 90-day exposure (8 h/day, 5 days/week) at various inhalation exposure concentrations.

study by Mahoney and Small (1968), subjects receiving 300–800 mg Mn/day had higher clearance rates than subjects on normal Mn diets alone. Similar observations were also made by Cotzias and Greenough (1958) who observed rapid <sup>54</sup>Mn clearance in mice receiving high doses of carrier Mn. These results were also consistent with those of Newland *et al.* (1987), where a monkey exposed to an sc tracer dose of <sup>54</sup>Mn with 400 mg of carrier Mn exhibited rapid clearance of the radiotracer. Clearance rates observed in this sc exposure were much faster than those seen following inhalation exposure (Newland *et al.*, 1987). Although Newland originally attributed these retention differences to a presumed slow-release Mn depot in the lung, it is more likely because of dose-dependent differences in Mn elimination caused by the large dose of carrier-free Mn. PBPK model simulations were able to accurately recapitulate all these dose-dependent scenarios by adjusting dietary absorption and controlling Mn tissue concentrations by dose-dependent inducible elimination rates.

Similar dose dependencies were observed in the case of inhalation exposure. Mena *et al.* (1967) examined clearance of an iv tracer dose of <sup>54</sup>Mn given to normal volunteers, healthy

Mn miners just removed from the mines, and in miners diagnosed with chronic Mn poisoning who had been removed from the mines several years prior to the study. Whole-body clearance of  $^{54}\text{Mn}$  was faster in the active miners than in the other groups presumably because of their elevated Mn body burden. Although the miners diagnosed with Mn poisoning had also worked in the mines, they were removed from the Mn exposures long enough that tissue Mn levels had likely returned to near normal, and thus, they exhibited clearance rates similar to those reported in healthy individuals. This behavior was also demonstrated with the human PBPK model by comparing simulated clearance of  $^{54}\text{Mn}$  in people exposed to different Mn exposure concentrations by inhalation (Fig. 12). In the model simulations, inhalation exposures started the day of the  $^{54}\text{Mn}$  iv injection and lasted for 60 days (8 h/day, 5 days/week). Simulated exposure concentrations were 0, 0.01, 0.1, and 1.0  $\text{mg}/\text{m}^3$ , spanning a range of concentrations that have been observed in human Mn exposure studies. At an exposure concentration of 0.01  $\text{mg}/\text{m}^3$ , there was virtually no change in  $^{54}\text{Mn}$  turnover from air-exposed controls. However, at the highest exposure concentration (1  $\text{mg}/\text{m}^3$ ), simulated  $^{54}\text{Mn}$  elimination was rapidly increased because of the higher body burden and increased biliary excretion of Mn from the inhalation exposures. These predictions in humans were also consistent with the findings of Dorman *et al.* (2001a) who found that rats exposed by inhalation to high Mn concentrations (0.3  $\text{mg Mn}/\text{m}^3$ ) had faster  $^{54}\text{Mn}$  clearance rates.

Tracer studies in rats, monkeys, and humans reveal similar findings: clearance behavior displays biphasic kinetics, there are dose route differences in elimination, and clearance rates depend on total Mn body burden either from Mn in diet or supplemental Mn exposures. Because tracer studies implicitly reflect the kinetics of Mn disposition, these studies reflect the dose dependencies of inducible biliary elimination on Mn levels in the body. The ability of the PBPK models to provide

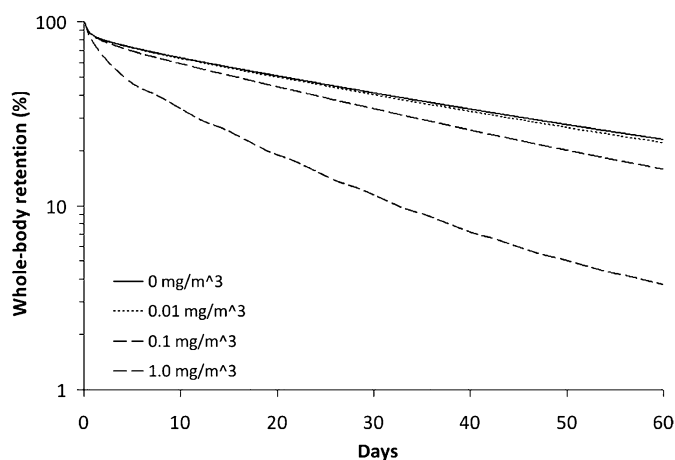


FIG. 12. Simulated effects of inhalation exposure to Mn particles on whole-body retention in humans given an iv dose of  $^{54}\text{Mn}$ .

consistent multispecies descriptions of Mn tracer kinetics across multiple exposure routes indicates that the models have captured the dose-dependent characteristics of Mn disposition and can accurately predict conditions where exposures will increase free Mn in various tissues throughout the body above background levels from normal dietary exposure.

The ability of the human PBPK model to predict Mn tissue dosimetry based on pharmacokinetic data in laboratory animals depends on a consistent description of Mn kinetics across species. There are significant physiological and biochemical differences between rats, monkeys, and humans that had to be accounted for in the interspecies PBPK models, including tissue volumes, blood flows, pulmonary ventilation, and less well-understood processes regulating Mn uptake and storage. Direct allometric scaling of model parameters from the rat was often not adequate to describe Mn tissue kinetics in other species. However, the availability of Mn pharmacokinetic time courses in multiple species and  $^{54}\text{Mn}$  clearance data in rats, monkeys, and humans allowed us to make further adjustments to model parameters beyond simple use of generic allometric scaling approaches to accurately describe Mn tissue dosimetry across multiple species. Although model parameters were changed beyond scaling, the underlying mechanisms governing Mn uptake and elimination (inducible biliary excretion, tissue-binding processes, and asymmetric diffusion fluxes) were preserved among species, providing confidence that a PBPK model with a consistent structure across species can accurately predict exposure conditions in humans that result in Mn tissue accumulation.

One of the primary species differences that affect Mn kinetics is diet. This difference is important to account for in the PBPK models because Mn is an essential nutrient. PBPK models for essential metals must account for dose-dependent biological processes that regulate absorption, tissue storage, and elimination. Concerns arise when exposure exceeds elimination capability. Laboratory animals are often maintained on diets that contain relatively high Mn concentrations, whereas the human diet is typically much lower in Mn (ranging from 1 to 10  $\text{mg}/\text{day}$ ). When Mn dietary intake is increased, homeostatic controls regulate Mn body burden by decreasing intestinal absorption and increasing biliary elimination. These processes were included in the PBPK model through use of the parameter  $F_{\text{dietup}}$ , which controls the amount absorbed by the GI tract, and  $k_{\text{bilec}}$ , which is the biliary excretion rate constant induced by Mn blood concentration. With higher Mn exposure, blood Mn concentrations increase, resulting in increased biliary elimination. The maximum induction factor implemented in the model was 2.5-fold, which was reached at higher exposure concentrations (1.5  $\text{mg}/\text{m}^3$ ).

Lung dose is an important determinant for subsequent Mn tissue dosimetry calculations resulting from inhalation exposure. Pulmonary ventilation and lung airway structure differ significantly between species. Deposition estimates for Mn

particles incorporated species-specific lung geometries, ventilatory rates, and particle properties by use of particle deposition software (MPPD) to estimate regional respiratory tract deposition. Because the monkey lung morphology was not available in MPPD, surface area scaling from the rat was used to obtain monkey respiratory tract deposition estimates. Deposition estimates using this scaling procedure were consistent with those reported by Cheng *et al.* (2008), where deposition of aerosol droplets was measured in the upper respiratory tract and lungs of monkeys.  $\text{MnSO}_4$  particles were used in this study because they were used in the monkey inhalation studies by Dorman *et al.* (2006a) and are more bioavailable than other less soluble forms (e.g.,  $\text{MnO}_2$  and  $\text{MnPO}_4$ ). Adjustments can be made to lung absorption parameters based on solubility to predict pharmacokinetics and dosimetry of other forms of Mn.

Another important difference between species is in the olfactory region. Whereas the rat olfactory epithelium comprises almost 50% of the total nasal surface area, in monkeys and humans, it is about 9 and 5%, respectively. This difference will influence the amount of Mn delivered to the olfactory bulb via the olfactory pathway. Olfactory delivery did not make a significant contribution to striatal Mn levels in the rat (Leavens *et al.*, 2007), and magnetic resonance imaging in nonhuman primates showed no significant signal intensities in the tissues connecting the olfactory bulb and midbrain regions (Dorman *et al.*, 2006b). These studies indicate that similar kinetic mechanisms may be at work in humans for delivery of Mn to the olfactory bulb. Nonetheless, the current model structure included olfactory transport in monkeys and humans even though the contribution of this route to midbrain tissues is minimal.

As inhalation exposure concentration increases, homeostatic controls associated with biliary elimination are overwhelmed by increased input rates because of pulmonary Mn absorption. At higher inhaled concentrations ( $> 0.1 \text{ mg/m}^3$ ), binding capacities and biliary clearance processes become saturated, allowing free Mn to accumulate in the tissues (Fig. 13). Tissue-binding rate constants ( $k_a$  and  $k_d$ ) and binding capacities ( $B_{\text{max}}$ ) determine the ratios of bound versus free Mn in each tissue. The most toxicologically relevant metric for human Mn neurotoxicity is likely tissue concentration of free Mn in the globus pallidus and other midbrain regions. A comparison of rat, monkey, and human predictions of Mn concentrations in the globus pallidus (and rat striatum) reveals that all species exhibited similar behavior upon increasing levels of inhalation exposure (Fig. 14), although the magnitude increases in brain Mn concentrations were slightly different among species. Predicted human globus pallidus Mn concentrations were less than those predicted in monkeys at exposure concentrations  $> 0.1 \text{ mg/m}^3$  but were very similar to those seen in the rat striatum. The larger magnitude changes predicted in monkeys compared with humans at higher inhalation exposure concentrations may be because of saturation of Mn binding sites in the

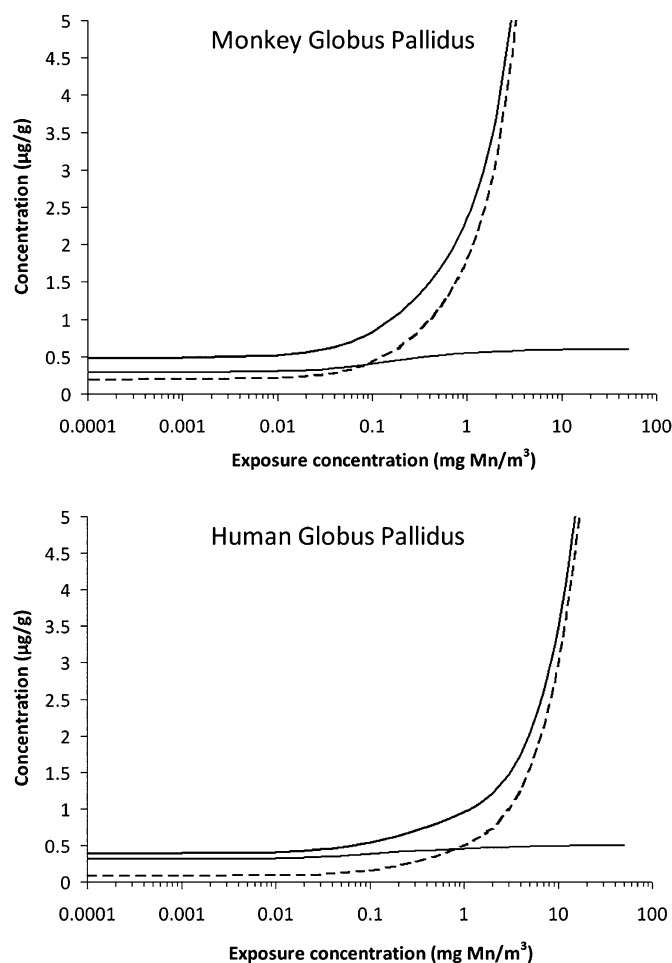


**FIG. 13.** Simulated end-of-exposure (90 days) Mn tissue concentrations of total (solid), free (dashed), and bound (gray) Mn in the monkey and human globus pallidus. The bound Mn fractions were 60 and 80% in the monkey and human, respectively, under normal dietary exposure.

monkey due to higher Mn concentrations in the diet. To test the sensitivity of Mn binding, further simulations were conducted assuming an equal bound Mn fraction (60% bound Mn fraction with no inhalation exposure) in humans and monkeys. Under these conditions, Mn globus pallidus concentrations in the human increased slightly faster than when an 80% bound fraction was used but still did not approach the levels observed in the monkey.

The human PBPK model can identify ranges of inhalation exposure concentrations where Mn levels in target tissues (specifically the globus pallidus) do not increase appreciably above background levels. Brain Mn concentrations begin to increase when subchronic (90 day) exposure concentrations rise to near  $0.1 \text{ mg Mn/m}^3$  (Fig. 14). This was also evident in the time course predictions (Fig. 11), showing negligible increases in globus pallidus Mn concentration in humans subject to an inhalation exposure concentration of  $0.01 \text{ mg/m}^3$  and tissue Mn levels increasing as exposure concentration increased. Predicted globus pallidus Mn concentrations

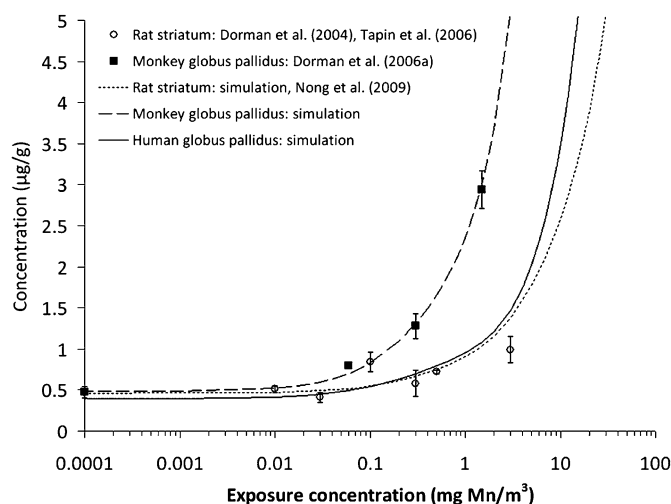


**FIG. 14.** Simulated end-of-exposure tissue Mn levels (total Mn) in the rat striatum and monkey and human globus pallidus. The simulated rat striatal Mn levels are from Nong *et al.* (2009) and are compared with data (mean  $\pm$  SE) from Dorman *et al.* (2004) and Tapin *et al.* (2006). The simulated monkey globus pallidus Mn levels are compared with data from Dorman *et al.* (2006a). Rats and monkeys were exposed to 6 h/day, 5 days/week for 90 days. Humans were exposed to 8 h/day, 5 days/week for 90 days.

increased slightly (by about 5%) over background levels at an exposure concentration of 0.1 mg/m<sup>3</sup> and increased dramatically for higher exposure concentrations. These data are consistent with derivations of benchmark concentrations for subclinical neurological effects from occupational studies at concentrations of 0.2 mg/m<sup>3</sup> (Clewett *et al.*, 2003).

## CONCLUSION

Risk assessments for Mn, as an essential element, should consider its essentiality as well as its toxicity. Homeostatic controls maintain relatively stable Mn tissue concentrations by regulating dietary absorption, compartmental transfer, and biliary excretion under low levels of Mn exposure. Toxicity may occur under conditions of excessive exposure when these

**TABLE 5**

**Dietary Absorption and Biliary Elimination Parameters Used in the Monkey <sup>54</sup>Mn Tracer Studies**

| Study                         | Body weight (kg) | Dose route | Mn diet (ppm)   | Fdietup | kbilec (l/h/kg) |
|-------------------------------|------------------|------------|-----------------|---------|-----------------|
| Dastur <i>et al.</i> (1971)   | 2.5              | ip         | 80 <sup>a</sup> | 0.00345 | 0.051           |
| Furchner <i>et al.</i> (1966) | 8.5              | iv         | 80              | 0.0017  | 0.051           |
| Furchner <i>et al.</i> (1966) | 7.0              | Oral       | 80              | 0.002   | 0.051           |
| Newland <i>et al.</i> (1987)  | 5.0              | sc         | 80 <sup>a</sup> | 0.0025  | 0.050           |
| Newland <i>et al.</i> (1987)  | 2.5–3.1          | Inhalation | 80 <sup>a</sup> | 0.001   | 0.015           |

<sup>a</sup>The Mn diet was not reported and was assumed to be 80 ppm for model simulations.

**TABLE 6**  
**Sensitivity Analysis of Peak Mn Concentration in the Globus Pallidus of Monkeys and Humans at Inhalation Exposure Concentrations of 0.01, 0.1, and 1.0 mg/m<sup>3</sup>. Normalized Sensitivity Parameters Reflect a 1% Change in Model Parameters**

| Model parameter     | Sensitivity coefficient |       |       |       |       |       |
|---------------------|-------------------------|-------|-------|-------|-------|-------|
|                     | Monkey                  |       |       | Human |       |       |
|                     | 0.01                    | 0.1   | 1.0   | 0.01  | 0.1   | 1.0   |
| Fdietup             | 0.96                    | 0.46  | 0.06  | 0.73  | 0.37  | 0.00  |
| kbile               | −0.96                   | −0.91 | −0.68 | −0.73 | −0.37 | −0.40 |
| Q <sub>tissue</sub> | 0.00                    | 0.00  | −0.03 | 0.00  | 0.00  | 0.00  |
| B <sub>max</sub>    | 0.57                    | 0.46  | 0.15  | 0.73  | 0.73  | 0.40  |
| k <sub>a</sub>      | 0.19                    | 0.11  | 0.00  | 0.24  | 0.18  | 0.00  |
| k <sub>d</sub>      | −0.38                   | −0.23 | −0.03 | −0.24 | −0.18 | −0.10 |
| k <sub>in</sub>     | 1.15                    | 1.37  | 1.18  | 0.73  | 0.55  | 0.60  |
| k <sub>out</sub>    | −1.34                   | −1.37 | −1.05 | −0.73 | −0.55 | −0.70 |
| k <sub>inmax</sub>  | 0.57                    | 0.91  | 0.99  | 0.49  | 0.55  | 0.50  |
| k <sub>in50</sub>   | −0.77                   | −0.68 | −0.34 | −0.24 | −0.18 | −0.10 |
| FdepLU <sup>a</sup> | 0.00                    | 0.11  | 0.43  | 0.00  | 0.18  | 0.20  |
| FdepNO <sup>b</sup> | 0.00                    | 0.00  | 0.03  | 0.00  | 0.00  | 0.00  |
| FdepNR <sup>c</sup> | 0.00                    | 0.11  | 0.25  | 0.00  | 0.18  | 0.10  |
| k <sub>GI</sub>     | 0.00                    | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  |
| F <sub>ent</sub>    | 0.00                    | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  |
| k <sub>ent</sub>    | 0.00                    | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  |

<sup>a</sup>Fractional deposition on lung epithelium.

<sup>b</sup>Fractional deposition on nasal olfactory epithelium.

<sup>c</sup>Fractional deposition on nasal respiratory epithelium.

homeostatic controls are overwhelmed. The PBPK models presented in this study account for background tissue levels associated with dietary exposure and simulate simultaneous exposure to Mn by ingestion and inhalation. Simulation results accurately recapitulated the rapid increase in tissue Mn from high inhalation concentrations and subsequent return to basal levels following inhalation exposures in monkeys and described clearance of tracer doses in monkeys and humans under normal dietary conditions and with supplemental Mn doses. The human model was validated against available Mn tracer data and was able to accurately capture Mn elimination dynamics following iv exposure to tracer Mn. Consistent interspecies descriptions of Mn kinetics show that the models can accurately predict exposure conditions that will result in increased tissue concentrations in humans and can be used in a dosimetry-based risk assessment (Andersen *et al.*, 1999) to identify exposure conditions that may lead to increased target tissue doses of this essential element.

## SUPPLEMENTARY DATA

Supplementary data are available online at <http://toxsci.oxfordjournals.org/>.

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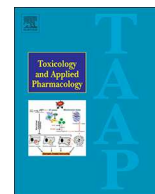
## REFERENCES

- Agency for Toxic Substances Disease Registry (ATSDR). (2000). *Toxicological Profile for Manganese*. U.S. Department for Health and Human Services, Public Health Service, Atlanta, GA.
- Andersen, M. E., Dorman, D. C., Clewell, H. J., III, Taylor, M. D., and Nong, A. (2010). Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment. *J. Toxicol. Environ. Health A* **73**, 217–234.
- Andersen, M. E., Gearhart, J. M., and Clewell, H. J., III. (1999). Pharmacokinetic data needs to support risk assessments for inhaled and ingested manganese. *Neurotoxicology* **20**, 161–171.
- Anjilvel, S., and Asgharian, B. (1995). A multiple-path model of particle deposition in the rat lung. *Fundam. Appl. Toxicol.* **28**, 41–50.
- Aschner, J. L., and Aschner, M. (2005). Nutritional aspects of manganese homeostasis. *Mol. Aspects Med.* **26**, 353–362.
- Aschner, M., Erikson, K. M., and Dorman, D. C. (2005). Manganese dosimetry: species differences and implications for neurotoxicity. *Crit. Rev. Toxicol.* **35**, 1–32.
- Asgharian, B., Hofmann, W., and Bergmann, R. (2001). Particle deposition in a multiple-path model of the human lung. *Aerosol. Sci. Technol.* **34**, 332–339.
- Bonilla, E., Salazar, E., Villasmil, J. J., and Villalobos, R. (1982). The regional distribution of manganese in the normal human brain. *Neurochem. Res.* **7**, 221–227.
- Borg, D. C., and Cotzias, G. C. (1958). Manganese metabolism in man: rapid exchange of  $Mn^{56}$  with tissue as demonstrated by blood clearance and liver uptake. *J. Clin. Invest.* **37**, 1269–1278.
- Brown, R. P., Delp, M. D., Lindstedt, S. L., Rhomberg, L. R., and Beliles, R. P. (1997). Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol. Ind. Health* **13**, 407–484.
- Bush, V. J., Moyer, T. P., Batts, K. P., and Parisi, J. E. (1995). Essential and toxic element concentrations in fresh and formalin-fixed human autopsy tissues. *Clin. Chem.* **41**, 284–294.
- Cheng, Y. S., Irshad, H., Kuehl, P., Holmes, T. D., Sherwood, R., and Hobbs, C. H. (2008). Lung deposition of droplet aerosols in monkeys. *Inhal. Toxicol.* **20**, 1029–1036.
- Clewell, H. J., Lawrence, G. A., Calne, D. B., and Crump, K. S. (2003). Determination of an occupational exposure guideline for manganese using the benchmark method. *Risk Analysis* **23**, 1031–1046.
- Conolly, R. B., Lilly, P. D., and Kimbell, J. S. (2000). Simulation modeling of the tissue disposition of formaldehyde to predict nasal DNA-protein cross-links in Fischer 344 rats, rhesus monkeys, and humans. *Environ. Health Perspect.* **108**(Suppl. 5), 919–924.
- Cotzias, G. C., and Greenough, J. J. (1958). The high specificity of the manganese pathway through the body. *J. Clin. Invest.* **37**, 1298–1305.
- Dastur, D. K., Manghani, D. K., and Raghavendran, K. V. (1971). Distribution and fate of  $^{54}Mn$  in the monkey: studies of different parts of the central nervous system and other organs. *J. Clin. Invest.* **50**, 9–20.
- Davidsson, L., Cederblad, A., Hagebo, E., Lonnerdal, B., and Sandstrom, B. (1988). Intrinsic and extrinsic labeling for studies of manganese absorption in humans. *J. Nutr.* **118**, 1517–1521.
- Davies, B., and Morris, T. (1993). Physiological parameters in laboratory animals and humans. *Pharm. Res.* **10**, 1093–1095.
- Davis, C. D., Wolf, T. L., and Greger, J. L. (1992). Varying levels of manganese and iron affect absorption and gut endogenous losses of manganese by rats. *J. Nutr.* **122**, 1300–1308.
- Dorman, D. C., McManus, B. E., Marshall, M. W., James, R. A., and Struve, M. F. (2004). Old age and gender influence the pharmacokinetics of inhaled manganese sulfate and manganese phosphate in rats. *Toxicol. Appl. Pharmacol.* **197**, 113–124.
- Dorman, D. C., Struve, M. F., James, R. A., Marshall, M. W., Parkinson, C. U., and Wong, B. A. (2001a). Influence of particle solubility on the delivery of inhaled manganese to the rat brain: manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure. *Toxicol. Appl. Pharmacol.* **170**, 79–87.
- Dorman, D. C., Struve, M. F., James, R. A., McManus, B. E., Marshall, M. W., and Wong, B. A. (2001b). Influence of dietary manganese on the pharmacokinetics of inhaled manganese sulfate in male CD rats. *Toxicol. Sci.* **60**, 242–251.
- Dorman, D. C., Struve, M. F., Marshall, M. W., Parkinson, C. U., James, A., and Wong, B. A. (2006a). Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. *Toxicol. Sci.* **92**, 201–210.
- Dorman, D. C., Struve, M. F., Wong, B. A., Dye, J. A., and Robertson, I. D. (2006b). Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. *Toxicol. Sci.* **92**, 219–227.
- Fell, J. M., Reynolds, A. P., Meadows, N., Khan, K., Long, S. G., Quaghebeur, G., Taylor, W. J., and Milla, P. J. (1996). Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* **347**, 1218–1221.
- Finkelstein, M. M., and Jerrett, M. (2007). A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. *Environ. Res.* **104**, 420–432.
- Finley, J. W. (1999). Manganese absorption and retention by young women is associated with serum ferritin concentration. *Am. J. Clin. Nutr.* **70**, 37–43.
- Finley, J. W., Johnson, P. E., and Johnson, L. K. (1994). Sex affects manganese absorption and retention by humans from a diet adequate in manganese. *Am. J. Clin. Nutr.* **60**, 949–955.
- Fitsanakis, V. A., Zhang, N., Garcia, S., and Aschner, M. (2010). Manganese (Mn) and iron (Fe) interdependency of transport and regulation. *Neurotoxicol. Res.* **18**, 124–131.
- Frederick, C. B., Bush, M. L., Lomax, L. B., Black, K. A., Finch, L., Kimbell, J. S., Morgan, K. T., Subramaniam, R. P., Morris, J. B., and Ultman, J. S. (1998). Application of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. *Toxicol. Appl. Pharmacol.* **152**, 211–231.
- Freeland-Graves, J. (1994). Derivation of manganese safe and adequate daily dietary intakes. In *Risk Assessment of Essential Elements* (W. Mertz, C. O. Abernathy, and S. S. Olin, Eds.), pp. 237–252. ILSI Press, Washington, DC.
- Furchner, J. E., Richmond, C. R., and Drake, G. A. (1966). Comparative metabolism of radionuclides in mammals. III. Retention of manganese-54 in the mouse, rat, monkey, and dog. *Health Phys.* **12**, 1415–1423.
- Iregren, A. (1990). Psychological test performance in foundry workers exposed to low levels of manganese. *Neurotoxicol. Teratol.* **12**, 673–675.



- Kawamura, R., Ikuta, H., Fukuzumi, S., Yamada, R., Tsubaki, S., Kodama, T., and Kurata, S. (1941). Intoxication by manganese in well water. *Arch. Exp. Med.* **18**, 145–169.
- Kepler, G. M., Richardson, R. B., Morgan, K. T., and Kimbell, J. S. (1998). Computer simulation of inspiratory nasal airflow and inhaled gas uptake in a rhesus monkey. *Toxicol. Appl. Pharmacol.* **150**, 1–11.
- Leavens, T. L., Rao, D., Andersen, M. E., and Dorman, D. C. (2007). Evaluating transport of manganese from olfactory mucosa to striatum by pharmacokinetic modeling. *Toxicol. Sci.* **97**, 265–278.
- Lucchini, R., Apostoli, P., Perrone, C., Placidi, D., Albin, E., Migliorati, P., Mergler, D., Sassine, M. P., Palmi, S., and Alessio, L. (1999). Long-term exposure to “low levels” of manganese oxides and neurofunctional changes in ferroalloy workers. *Neurotoxicology* **20**, 287–297.
- Lucchini, R., Selis, L., Folli, D., Apostoli, P., Mutti, A., Vanoni, O., Iregren, A., and Alessio, L. (1995). Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure. *Scand. J. Work Environ. Health* **21**, 143–149.
- Lucchini, R. G., Albin, E., Benedetti, L., Borghesi, S., Coccaglio, R., Malara, E. C., Parrinello, G., Garattini, S., Resola, S., and Alessio, L. (2007). High prevalence of Parkinsonian disorders associated to manganese exposure in the vicinities of ferroalloy industries. *Am. J. Ind. Med.* **50**, 788–800.
- Mahoney, J. P., and Small, W. J. (1968). Studies on manganese III. The biological half-life of radiomanganese in man and factors which affect this half-life. *J. Clin. Invest.* **47**, 643–653.
- Mena, I., Marin, O., Fuenzalida, S., and Cotzias, G. C. (1967). Chronic manganese poisoning: clinical picture and manganese turnover. *Neurology* **17**, 128–136.
- Menache, M. G., Hanna, L. M., Gross, E. A., Lou, S. R., Zinreich, S. J., Leopold, D. A., Jarabek, A. M., and Miller, F. J. (1997). Upper respiratory tract surface areas and volumes of laboratory animals and humans: considerations for dosimetry models. *J. Toxicol. Environ. Health* **50**, 475–506.
- Mergler, D., Baldwin, M., Belanger, S., Larribe, F., Beuter, A., Bowler, R., Panisset, M., Edwards, M., de Geoffroy, A., Sassine, M. P., et al. (1999). Manganese neurotoxicity, a continuum of dysfunction: Results from a community based study. *Neurotoxicology* **20**, 327–342.
- Mergler, D., Huel, G., Bowler, R., Iregren, A., Belanger, S., Baldwin, M., Tardif, R., Smargiassi, A., and Martin, L. (1994). Nervous system dysfunction among workers with long-term exposure to manganese. *Environ. Res.* **64**, 151–180.
- Molokhia, M. M. (1967). Trace elements in the lung. *Arch. Environ. Health* **15**, 745–750.
- Myers, J. E., Thompson, M. L., Ramushu, S., Young, T., Jeebhay, M. F., London, L., Esswein, E., Renton, K., Spies, A., Boule, A., et al. (2003). The nervous system effects of occupational exposure on workers in a South African manganese smelter. *Neurotoxicology* **24**, 885–894.
- Newland, M. C., Cox, C., Hamada, R., Oberdorster, G., and Weiss, B. (1987). The clearance of manganese chloride in the primate. *Fundam. Appl. Toxicol.* **9**, 314–328.
- Nong, A., Taylor, M. D., Clewell, H. J., III, Dorman, D. C., and Andersen, M. E. (2009). Manganese tissue dosimetry in rats and monkeys: accounting for dietary and inhaled Mn with physiologically based pharmacokinetic modeling. *Toxicol. Sci.* **108**, 22–34.
- Nong, A., Teeguarden, J. G., Clewell, H. J., III, Dorman, D. C., and Andersen, M. E. (2008). Pharmacokinetic modeling of manganese in the rat IV: assessing factors that contribute to brain accumulation during inhalation exposure. *J. Toxicol. Environ. Health A* **71**, 413–426.
- Pal, P. K., Samii, A., and Calne, D. B. (1999). Manganese neurotoxicity: a review of clinical features, imaging and pathology. *Neurotoxicology* **20**, 227–238.
- Rodriguez-Agudelo, Y., Riojas-Rodriguez, H., Rios, C., Rosas, I., Sabido Pedraza, E., Miranda, J., Siebe, C., Texcalac, J. L., and Santos-Burgoa, C. (2006). Motor alterations associated with exposure to manganese in the environment in Mexico. *Sci. Total Environ.* **368**, 542–556.
- Roels, H., Lauwerys, R., Buchet, J. P., Genet, P., Sarhan, M. J., Hanotiau, I., de Fays, M., Bernard, A., and Stancu, D. (1987). Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. *Am. J. Ind. Med.* **11**, 307–327.
- Roels, H. A., Ghyselen, P., Buchet, J. P., Ceulemans, E., and Lauwerys, R. R. (1992). Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Br. J. Ind. Med.* **49**, 25–34.
- Roels, H. A., Ortega Eslava, M. I., Ceulemans, E., Robert, A., and Lison, D. (1999). Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. *Neurotoxicology* **20**, 255–271.
- Schroeter, J. D., Garcia, G. J. M., and Kimbell, J. S. (2010). A computational fluid dynamics approach to assess interhuman variability in hydrogen sulfide nasal dosimetry. *Inhal. Toxicol.* **22**, 277–286.
- Schroeter, J. D., Kimbell, J. S., Gross, E. A., Willson, G. A., Dorman, D. C., Tan, Y. M., and Clewell, H. J., III. (2008). Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein. *Inhal. Toxicol.* **20**, 227–243.
- Spahr, L., Butterworth, R. F., Fontaine, S., Bui, L., Therrien, G., Milette, P. C., Lebrun, L. H., Zayed, J., Leblanc, A., and Pomier-Layrargues, G. (1996). Increased blood manganese in cirrhotic patients: relationship to pallidal magnetic resonance signal hyperintensity and neurological symptoms. *Hepatology* **24**, 1116–1120.
- Sumino, K., Hayakawa, K., Shibata, T., and Kitamura, S. (1975). Heavy metals in normal Japanese tissues. *Arch. Environ. Health* **30**, 487–494.
- Tapin, D., Kennedy, G., Lambert, J., and Zayed, J. (2006). Bioaccumulation and locomotor effects of manganese sulfate in Sprague-Dawley rats following subchronic (90 days) inhalation exposure. *Toxicol. Appl. Pharmacol.* **211**, 166–174.
- Teeguarden, J. G., Dorman, D. C., Covington, T. R., Clewell, H. J., III, and Andersen, M. E. (2007a). Pharmacokinetic modeling of manganese. I. Dose dependencies of uptake and elimination. *J. Toxicol. Environ. Health A* **70**, 1493–1504.
- Teeguarden, J. G., Dorman, D. C., Nong, A., Covington, T. R., Clewell, H. J., III, and Andersen, M. E. (2007b). Pharmacokinetic modeling of manganese. II. Hepatic processing after ingestion and inhalation. *J. Toxicol. Environ. Health A* **70**, 1505–1514.
- Teeguarden, J. G., Gearhart, J., Clewell, H. J., III, Covington, T. R., Nong, A., and Andersen, M. E. (2007c). Pharmacokinetic modeling of manganese. III. Physiological approaches accounting for background and tracer kinetics. *J. Toxicol. Environ. Health A* **70**, 1515–1526.
- Thorlacius-Ussing, O., Gregersen, M., and Hertel, N. (1988). The concentration of twelve elements in the anterior pituitary from human subjects and rats as measured by particle induced x-ray emission (PIXE). *Biol. Trace Element Res.* **16**, 189–202.
- Tracqui, A., Tayot, J., Kintz, P., Alves, G., Bosque, M. A., and Mangin, P. (1995). Determination of manganese in human brain samples. *Forensic Sci. Int.* **76**, 199–203.
- Vitarella, D., Moss, O., and Dorman, D. C. (2000). Pulmonary clearance of manganese phosphate, manganese sulfate, and manganese tetroxide by CD rats following intratracheal instillation. *Inhal. Toxicol.* **12**, 941–957.
- Yamada, M., Ohno, S., Okayasu, I., Okeda, R., Hatakeyama, S., Watanabe, H., Ushio, K., and Tsukagoshi, H. (1986). Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain. *Acta Neuropathol.* **70**, 273–278.
- Yoon, M., Nong, A., Clewell, H. J., Taylor, M. D., Dorman, D. C., and Andersen, M. E. (2009a). Evaluating placental transfer and tissue

- concentrations of manganese in the pregnant rat and fetuses after inhalation exposures with a PBPK model. *Toxicol. Sci.* **112**, 44–58.
- Yoon, M., Nong, A., Clewell, H. J., Taylor, M. D., Dorman, D. C., and Andersen, M. E. (2009b). Lactational transfer of manganese in rats: predicting manganese tissue concentration in the dam and pups from inhalation exposure with a pharmacokinetic model. *Toxicol. Sci.* **112**, 23–43.
- Young, T., Myers, J. E., and Thompson, M. L. (2005). The nervous system effects of occupational exposure to manganese—measured as respirable dust—in a South African manganese smelter. *Neurotoxicology* **26**, 993–1000.



# Updating physiologically based pharmacokinetic models for manganese by incorporating rapid association/dissociation processes in tissues

Miyoung Yoon<sup>a,b,\*</sup>, Alina Efremenko<sup>a</sup>, Cynthia Van Landingham<sup>c</sup>, P. Robinan Gentry<sup>c</sup>, Athena M. Keene<sup>d</sup>, Michael D. Taylor<sup>e</sup>, Harvey J. Clewell<sup>a,c</sup>, Melvin E. Andersen<sup>a</sup>

<sup>a</sup> ScitoVation, LLC, RTP, Cary, NC, USA

<sup>b</sup> Toxstrategies, Inc., Cary, NC, USA

<sup>c</sup> Ramboll, RTP, NC, USA

<sup>d</sup> Afton Chemical, Richmond, VA, USA

<sup>e</sup> NIPERA, RTP, NC, USA

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## ABSTRACT

Previously, we developed a series of physiologically based pharmacokinetic (PBPK) models for manganese (Mn) in which saturable tissue binding and dose-dependent increases in biliary excretion captured key aspects of Mn homeostasis biology. These models reproduced the non-linear behavior of Mn kinetics in different tissues, accounting for dose-dependent changes in Mn kinetics. The original model construct had relatively slow association and dissociation rate constants for Mn binding in tissues. In this updated model, both rates of entry into tissue and the interaction of Mn with binding sites are rapid, and the step limiting Mn accumulation is the saturation of tissue binding sites. This binding reflects general cellular requirements for Mn with high affinity but rapid exchange between bound and free forms, which we captured using a dissociation constant (KD) of  $\sim 0.5 \mu\text{M}$  across tissues while maintaining different maximum binding capacities in each tissue. Variability in the binding capacities accounted for different background levels of Mn in particular tissues. This alternative structure successfully described Mn kinetics in tissues in adult rats exposed to Mn either in their diet or by inhalation, indicating that both the original and the present models capture the dose-dependent and tissue-specific kinetic behavior of Mn in adult rats. Although the published models that emphasize the role of smaller tissue binding rate constants in non-linear behaviors capture all relevant dose-dependent kinetic behaviors of this metal, increasing biological relevance of the model structure and parameters should provide greater confidence in applying the Mn PBPK models to risk assessment.

## 1. Introduction

Mn is an essential element and present in all tissues in significant concentrations. The best-known role of Mn in the body is as a redox-active cofactor in the cellular antioxidant defense enzymes such as Mn-superoxide dismutase (Aschner et al., 2007). Tissue Mn concentrations are maintained at a relatively constant level despite widely varying levels of Mn input from dietary intake ranging from 1 to 10 mg Mn per day in humans (ATSDR, 2013; Freeland-Graves, 1994). This tight control of body Mn is attributable to multiple homeostatic processes: 1) uptake in the gut, 2) storage and utilization in the tissue, and 3) biliary excretion (Aschner et al., 2005; Teeguarden et al., 2007). However, exposure to excessive Mn such as chronic inhalation of high doses Mn (over 1 mg Mn/m<sup>3</sup>) can overwhelm the homeostasis leading to toxicity

in the central nervous system (CNS) (Andersen et al., 2010; Roels et al., 1999). Other excessive exposure conditions such as long-term parenteral nutrition containing Mn and/or impaired Mn clearance due to liver dysfunction can also compromise homeostatic regulation of Mn and lead to elevated CNS target tissue concentration (Leyva-Illades et al., 2014; Santos et al., 2014).

A series of PBPK models has been developed for Mn considering both essentiality and toxicity to support a human health risk assessment of Mn exposure (Nong et al., 2009; Schroeter et al., 2011; Yoon et al., 2011). The models are intended to predict exposure conditions that would lead to toxicologically significant increases in Mn concentrations in the target tissue compared to the levels maintained with normal dietary intake. These models are based on the knowledge of the biological factors that control uptake, distribution, and clearance of Mn

\* Corresponding author at: ToxStrategies, Inc., 1249 Kildaire Farm Road #134, Cary, North Carolina 27511, USA.

E-mail address: [yoon.m.work@gmail.com](mailto:yoon.m.work@gmail.com) (M. Yoon).

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and other essential trace metals that were available at the time of model development. To describe the dose-dependent pharmacokinetic behavior of Mn observed in multi-dose, multi-route and multi-species pharmacokinetic studies, it was necessary to describe Mn homeostasis as the underlying reason for those dose-dependent kinetics behavior (Andersen et al., 2010). The introduction of these biological processes was accomplished using the concept of saturable tissue binding and inducible biliary excretion.

The published models effectively reproduced the non-linear behavior of Mn kinetics in different tissues. However, the knowledge gained about Mn homeostasis in recent years indicates that metal homeostasis depends primarily on regulation of uptake into and efflux out of tissues via various cellular membrane metal transporters and less on avid binding of Mn within tissues (Aschner and Erikson, 2017; Chen et al., 2015). Recent studies have shown that several of the zinc transporter proteins are crucial in Mn homeostasis in addition to those already known such as the divalent metal transporter 1 (DMT1) and transferrin/transferrin receptor system. Notably, SLC30A10, SLC39A8 and SLC39A14 have shown to be pivotal in Mn clearance and maintenance of Mn homeostasis in vertebrates (Chen et al., 2015; Leyva-Illades et al., 2014; Lin et al., 2017; Tuschl et al., 2016). Compared to Mn importers, transporters for Mn efflux and the underlying mechanisms of Mn efflux and their role in maintaining Mn homeostasis in mammalian systems have been discovered only recently. Among those, SLC30A10 appear to be the most relevant Mn efflux transporters playing a role in mediating Mn efflux in neuronal systems (Chen et al., 2015; Hutchens et al., 2017; Leyva-Illades et al., 2014).

In this study, we evaluated an alternative model structure that is more consistent with the recent understanding of the biology of essential metal transport across the cell membrane through metal transporters rather than one relying on the description of tissue binding processes controlling elimination rates for Mn. While the published models have successfully served their roles in supporting internal exposure-based Mn risk assessment, the new model structure will facilitate the incorporation of data from emerging in vitro and in vivo models on Mn transport, enabling the mechanism-based refinement of the model structure, and should lead to increased confidence in model applications.

## 2. Materials and methods

### 2.1. Model structure

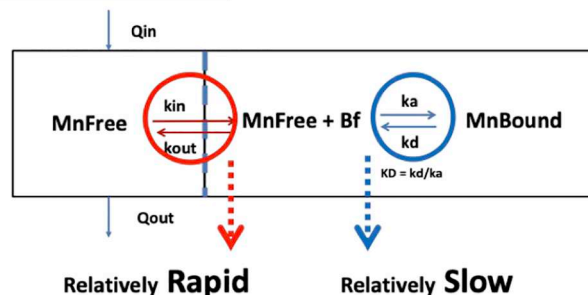
Two rat Mn PBPK models are compared in this study (Fig. 1). The published model (Nong et al., 2008) is referred as ‘binding’ or ‘original’ model, whereas the model newly introduced here is referred to as ‘transporter’, ‘rapid binding/dissociation’ or ‘updated’ model. Note that saturable tissue storage and asymmetric diffusion in and out of the tissue are key determinants of tissue Mn in both models (Fig. 1). Only the relative rates of these processes are different between the two models. Therefore, this update of the model can be viewed as a reparameterization of the original model described in Nong et al. (2008).

#### 2.1.1. Original model

The basic structure of the existing PBPK models describing Mn kinetics in multi-species with multi-exposure routes for rodents, primates and humans is based on the ‘original’ model developed in the rat (Nong et al., 2009). Most of the features in the Nong model were maintained in the updated model. Only the features that are notably different in the new model are detailed below. For other details of the published model, Nong et al. (2009) should be referred to.

Briefly, Mn is rapidly cleared into the tissues after entering the systemic circulation regardless of exposure routes. For brain, this clearance was described as an asymmetric bi-directional diffusion. The free Mn in systemic blood rapidly equilibrates with free Mn in the blood of the brain tissue. The flux between brain tissue-blood and brain tissue

### A. Original model



### B. Updated model

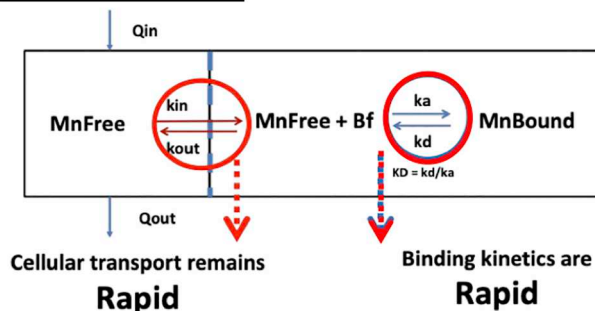


Fig. 1. Model structure: slow (A) versus rapid binding (B) reactions in tissues. The kin and kout represent diffusion rate constants for Mn influx and efflux, respectively, while the ka and kd represent association and dissociation rate constants.

Mn total = MnFree + MnBound, whereas Bmax = Bf + MnBound.

Bf represents binding sites that are available for binding, while Bmax represents the maximum binding capacity in a tissue.

is diffusion limited, the rate of which is determined by the diffusion rate constants, kin and kout, respectively. In the original model, the diffusion limitation in the brain was considered to reflect the role of blood-brain barrier in controlling Mn in and out fluxes.

The feature of asymmetrical diffusion was included in a brain region-specific fashion, a decision that was rationalized due to different requirements for basal manganese in different regions and differential distribution of transporters. The asymmetrical diffusion is necessary to describe the preferential uptake of Mn into the mid-brain seen with high levels of Mn exposure. For other tissues, a rapid and symmetrical flux of Mn between the systemic blood and tissue compartment was included using a partition coefficient, and thus, the tissue Mn in these other tissue compartments is primarily determined by the tissue binding characteristics.

Once distributed into the tissue, Mn is ‘bound’ to the cellular components that require Mn for a variety of biological functions, i.e., utilized in the cell. Bound Mn is not readily available to diffuse from tissue to blood. The ‘binding’ capacity, therefore, represents a total pool of accessible binding partners for manganese. The model structure does not attempt to differentiate between different enzymes, proteins, etc. with which Mn associates within tissues. The incorporation of Mn into these cellular proteins/tissue constituents and subsequent loss from those ‘binding sites’ back to blood are governed by three model parameters - maximum tissue binding capacity (Bmax) and tissue specific association and dissociation rate constants (ka and kd, respectively). Initial estimates of Bmax were based on the basal levels of manganese in various tissues.

The fraction bound (or fraction free) in the tissue varies dependent on the Mn content in diet at steady-state. At normal dietary intakes, the majority of Mn in the tissue will be associated with cellular

**Table 1**  
Model parameters.

| Nong model     | Bmax <sup>a</sup><br>(uM) | KD (uM) | ka<br>(/uM/h) | kd (/h)        | Kin<br>(ml/h) | Kout<br>(ml/h) |
|----------------|---------------------------|---------|---------------|----------------|---------------|----------------|
| Striatum       | 21                        | 9.89    | 1.3           | <b>0.001</b>   | 0.13          | 0.10           |
| Cerebellum     | 19                        | 0.01    | 70.2          | <b>0.00013</b> | 0.08          | 2.48           |
| Olfactory blub | 35                        | 0.16    | 32.4          | <b>0.0003</b>  | 0.02          | 0.19           |
| Liver          | 43                        | 0.07    | 14.6          | <b>0.0111</b>  | N/A           | N/A            |
| Bone           | 11                        | 4.04    | 0.2           | <b>0.0238</b>  | N/A           | N/A            |
| Lung           | 270                       | 43.17   | 5.4           | <b>0.38</b>    | N/A           | N/A            |
| Rest of body   | 4                         | 0.03    | 0.5           | <b>0.00454</b> | N/A           | N/A            |

| Updated model  | Bmax <sup>a</sup><br>(uM) | KD (uM) | ka (/uM/h) | kd (/h)    | Kin<br>(ml/h) | Kout<br>(ml/h) |
|----------------|---------------------------|---------|------------|------------|---------------|----------------|
| Striatum       | 15                        | 0.46    | 10         | <b>4.6</b> | 0.08          | 0.10           |
| Cerebellum     | 9                         | 0.37    | 10         | <b>3.7</b> | 0.08          | 0.44           |
| Olfactory blub | 4                         | 0.46    | 10         | <b>4.6</b> | 0.08          | 0.05           |
| Liver          | 46                        | 0.46    | 10         | <b>4.6</b> | 3.95          | 36.9           |
| Bone           | 20                        | 0.46    | 10         | <b>4.6</b> | 0.01          | 0.63           |
| Lung           | 15                        | 0.46    | 10         | <b>4.6</b> | 0.77          | 16.1           |
| Rest of body   | 4                         | 0.37    | 10         | <b>3.7</b> | 0.01          | 1.33           |

Parameters used in the original model with small, fitted tissue dissociation rate constants (top) and the revised model that uses a common tissue equilibrium dissociation constant for Mn binding across tissues and more rapid Mn-dissociation rate constants (bottom). N/A denotes 'not applicable' as these parameters were not used, but the partition coefficients were used instead in the original model for these tissues. More rapid Mn-dissociation rate constants are used in the revised model than the original model are highlighted in bold.

<sup>a</sup> Tissue binding capacity is study specific, although the same values were used most of the studies. A few occasions they were varied from the listed Bmax values in this table to fit the observed basal tissue concentrations in the specific studies if necessary (see Table S1 in Supplementary materials for cerebellum, lung and liver).

constituents, i.e., 'bound'. With sufficiently high Mn in diet, the fraction of Mn in the tissue in a bound form, i.e., Mn<sub>bound</sub>/(Mn<sub>bound</sub> + Mn<sub>free</sub>), would be lower than the same ratio in animals on a marginal Mn diet. The fraction bound expressed in this manner does not directly represent the actual occupancy of binding sites. In high-dose exposure, binding sites would be eventually saturated, and the fraction free could exceed the fraction bound. In such cases, free Mn – the form believed to be related to effects in target tissues – increases disproportionately compared to the increase in external dose.

Free Mn circulates in blood and is the form excreted into bile. The bound form is in the tissue and dissociates from the binding sites with a rate constant kd. A key factor differentiating the two models is the magnitude of kd: it was smaller in the original model and larger in the updated model.

### 2.1.2. The updated model

In the original model, dissociation of bound forms of Mn was slow (Table 1) and designed to be the limiting process for loss of Mn when body and tissue stores were reduced by alterations in intake or at the end of high dose exposures. In this updated model, the dissociation (and association) rate constants are much larger and tissue stores adjust more rapidly to alterations in Mn intake and total body burden.

These higher rates of tissue binding and the consistency of the dissociation equilibrium constant across tissues are more reflective of the biology of interactions of Mn with tissue proteins. The use of a common dissociation constant (KD) at 0.5  $\mu$ M is more consistent with similarities in Mn utilization and requirements across tissue types and leads to maintenance of Mn in bound forms until the binding sites become saturated. The variability in the presumed binding capacities across tissues still accounts for different background levels of Mn in particular tissues as in the Nong et al. (2008) model, as they reflect differing degrees of Mn demands among different tissues. Using a KD of approximately 0.5  $\mu$ M for all tissues, about 70% of Mn in tissues in the

basal state is bound.

## 2.2. Model parameterization

All the physiological and chemical-specific parameters other than those updated (Table 1) were kept the same as the previously published binding model (Nong et al., 2008).

In our revised model, uptake of Mn to all the tissues, not just brain regions, is mediated by a tissue uptake rate constant rather than blood flow directly. This membrane transport is tissue dependent allowing differential increases in Mn in the target tissues after high-dose-rate exposures of Mn. Describing all transport as linear processes captured the kinetics both for steady-state and inhalation exposure conditions, i.e., there is no need to introduce dose-dependent transport rate constants across cellular membranes.

To convert parameter values from the original to the updated model, the following steps were taken. Briefly, the association rate constant (ka) was set at 10/ $\mu$ M/h to allow rapid complexing of Mn to binding partners in all the tissues. The corresponding dissociation rate constant (kd) was calculated to obtain a KD of around 0.5  $\mu$ M in all the tissues. The uptake rate constant parameter (KinC) was set to give smaller uptake clearances (Kin in the unit of ml/h) for brain and bone (i.e., limited uptake), and higher uptake clearances for other tissues, in particular for liver (Table 1). Efflux parameters (KoutC) for each tissue were fitted to be consistent with the tissue concentrations both during steady-state conditions and during inhalation exposures that increase tissue Mn.

The new model could recapitulate dose-dependent increases in biliary excretion without biliary induction, and so the model structure was finalized as such.

## 2.3. Model evaluation and sensitivity analysis

### 2.3.1. Experimental data used for model evaluation

To compare the performance of the original and the updated models, three data sets from rat pharmacokinetic studies were used. They were collected both in steady-state dietary and inhalation exposure conditions and were used for model development and evaluation of the original model as well. A brief description of these studies is given below.

- *Steady-state dietary exposure study* - Rats were maintained on a diet containing Mn at 2, 10, and 100 ppm for over 11 weeks. Both tissue steady-state Mn concentrations and elimination kinetics for an intravenous tracer administration of <sup>54</sup>MnCl<sub>2</sub> without inhalation exposure data were reported and used for model evaluation (Dorman et al., 2001a).
- *Fourteen-day inhalation study* - Rats were exposed to soluble MnSO<sub>4</sub> at concentrations of 0, 0.03, 0.3 or 3 mg Mn/m<sup>3</sup> for 14 consecutive days for 6 h/day in addition to a 125 ppm (approximately 100–150 ppm) dietary Mn exposure. Tissue concentrations of Mn as well as the <sup>54</sup>Mn tracer (which was administered at the end of the 14 day inhalation exposure) kinetics at the end of the 14 day exposure period from this study were used for model evaluation (Dorman et al., 2001b).
- *Ninety-day inhalation study* - Rats were fed a 10 ppm Mn diet and exposed via inhalation to MnSO<sub>4</sub> at concentrations of 0.1 or 0.5 mg/m<sup>3</sup> for 6 h/day and 5 days/week with weekends off, over a 90-day period. Tissue Mn concentrations were reported at 45- and 90-day after the cessation of the inhalation exposure (Dorman et al., 2004).

### 2.3.2. Sensitivity analysis

A sensitivity analysis of the original and the updated models was performed for 6 key model parameters, ones that had been shown to have a high sensitivity for striatal Mn in the original model (Nong et al., 2008). The 6 parameters included influx and efflux rates into and out of



the striatum (KINSTC and KOUTSTC), association and dissociation rate constants in the striatum (KAST and KDST), the biliary excretion rate constant (KBILEC), and the absorption fraction in the gut (FDIETUP). The relative importance of these parameters in determining the total Mn concentration in the brain striatum region (CTOTST) or the amount of remaining tracer Mn (ATOT54) in the whole body was evaluated as described in earlier studies (Nong et al., 2008; Yoon et al., 2011). The sensitivity coefficients of 0.1 or greater are reported.

#### 2.4. Model simulations

All the model simulations were run using acslX (version 3.0.2.1; The Aegis Technologies Group, Inc., Huntsville, Alabama). Model fitting/parameter optimization was performed using the automated parameter optimization function in acslX based on NelderMead algorithm. The model code is available from the corresponding author upon request.

### 3. Results

#### 3.1. Simulation of whole-body Mn tracer kinetics in steady-state and inhalation exposure

The time course of the intravenously injected  $^{54}\text{Mn}$  elimination kinetics was determined in rats on three different diets, containing Mn at 2, 10 or 100 ppm, at steady-state (Dorman et al., 2001a). The simulation of the loss of  $^{54}\text{Mn}$  from the body was fairly well described with either the original parameters or with the updated model structure (Fig. 2). A second tracer study was conducted in rats exposed to various concentrations of  $\text{MnCl}_2$  by inhalation for 14 days in rats fed on an approximately 125 ppm diet (Dorman et al., 2001b). The tracer was administered intravenously at the end of the 14-day inhalation exposure; hence the tracer kinetics reflected how the total amount of Mn in the body changes immediately after the inhalation exposure stops. The updated model with rapid binding provided a slightly better fit to both the more rapid initial loss of Mn from the body and maintenance of tracer Mn at the later times at the three different dietary intakes (Fig. 4). As with diet alone, the rapid binding/dissociation model provided a more accurate description of the loss of tracer over time as the body returned to a basal condition after brief periods of high concentration exposure to Mn via tracer injection (Figs. 3 and 4).

#### 3.2. Simulation of brain Mn kinetics in steady-state and inhalation exposure

The simulated striatum concentrations from both models were consistent with the observed total tissue Mn concentrations at steady state following administration of dietary Mn concentrations ranging from 2 to 100 ppm in the Dorman et al. (2001b) study (Fig. 5). Also, both models reproduced the observed striatum Mn concentrations at the end of the 14 day inhalation exposure (Fig. 5) reported in Dorman et al. (2001a). The updated model produced a more rapid rise in striatum Mn along with a greater daily fluctuation over the time course of the simulation. Similarly, the updated model performed marginally better in capturing the time profiles of striatum Mn after 90 day inhalation exposure (Fig. 5C). In particular, the updated model was able to better recapitulate a time profile of rapid elimination and return to steady state after the cessation of the last inhalation dosing as was shown with 0.5 mg Mn/m<sup>3</sup>.

#### 3.3. Comparison of the simulated Mn kinetics in free and bound Mn forms

Figs. 5 and C clearly showed that the updated model shows more extensive short-term excursions, although both models recapitulated the observed tissue concentrations during and at the end of inhalation exposure equally well. Updated model simulated striatum Mn kinetics in free vs. bound forms were plotted (Fig. 6) showing that striatum Mn time profiles are predominantly determined by the increase in free Mn in the updated model. This was also the case in the original model (Nong et al., 2009), although with much less short term excursions, particularly in the later refined original model (Nong et al., 2008) as is shown in Fig. 5-A.

#### 3.4. Sensitivity analysis of binding and transporter model parameters

The results of the sensitivity analysis of the updated and the published original models performed for the 6 key model parameters that were shown to be highly influential to striatum Mn concentrations in the binding model were plotted for steady state (Fig. 7A), 14-day inhalation (Fig. 7B) and 90-day inhalation (Fig. 7C). In contrast to the earlier model sensitivity analysis, the updated model with more rapid binding and dissociation shows significant sensitivity for both the uptake and efflux rate constants in and out of the striatum, whereas with the original model, the striatum Mn concentration is sensitive to both transport and binding rates.

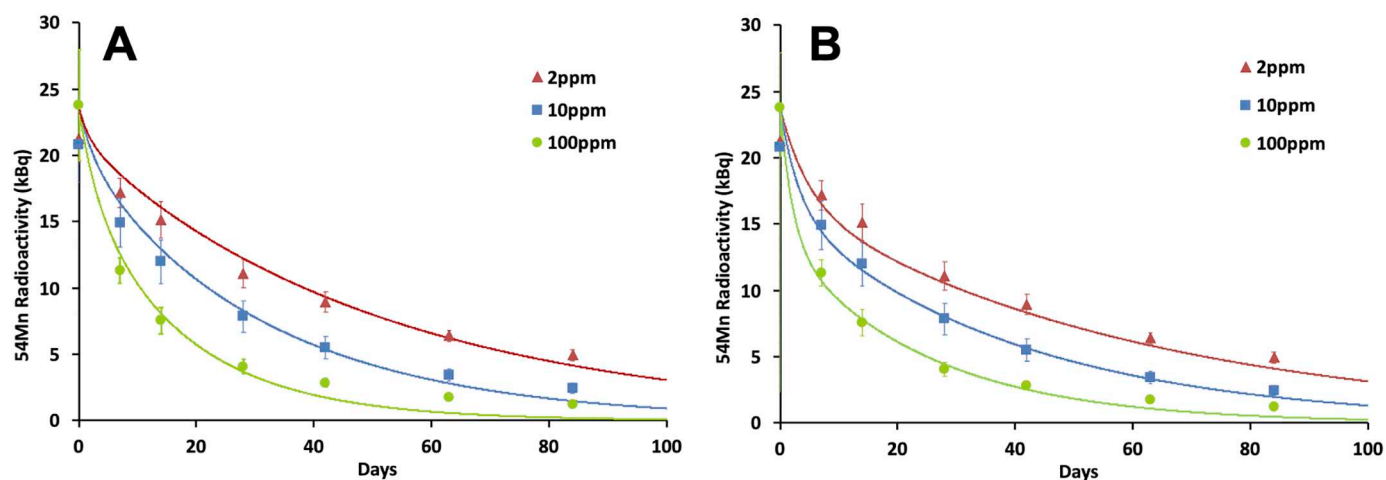


Fig. 2. Steady-state tracer kinetics. Symbols represent the mean  $\pm$  SD from the data by Dorman et al. (2001a) of the individual animals, whereas the lines in corresponding colors represent model simulations using the published (A) or updated (B) model for  $^{54}\text{Mn}$  tracer total body radioactivity in rats fed on a 2, 10 or 100 ppm Mn diet for 13 weeks in the same study. Intravenous injection of  $^{54}\text{MnCl}_2$  was done following the 13-week diet, and the whole-body Mn radioactivity was measured for 10 weeks post-injection exposure.

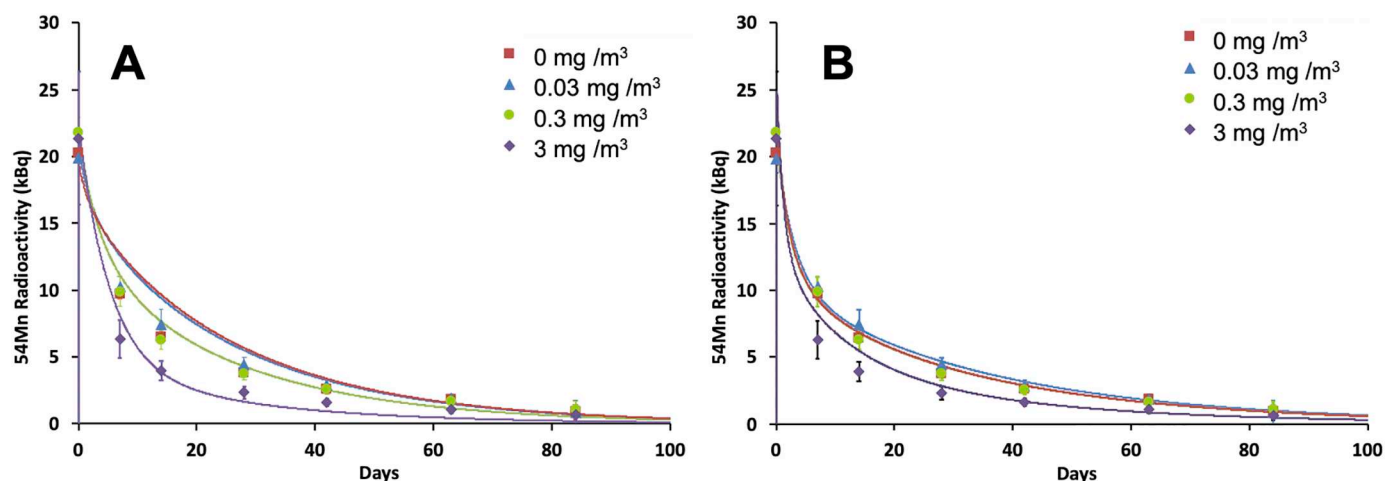


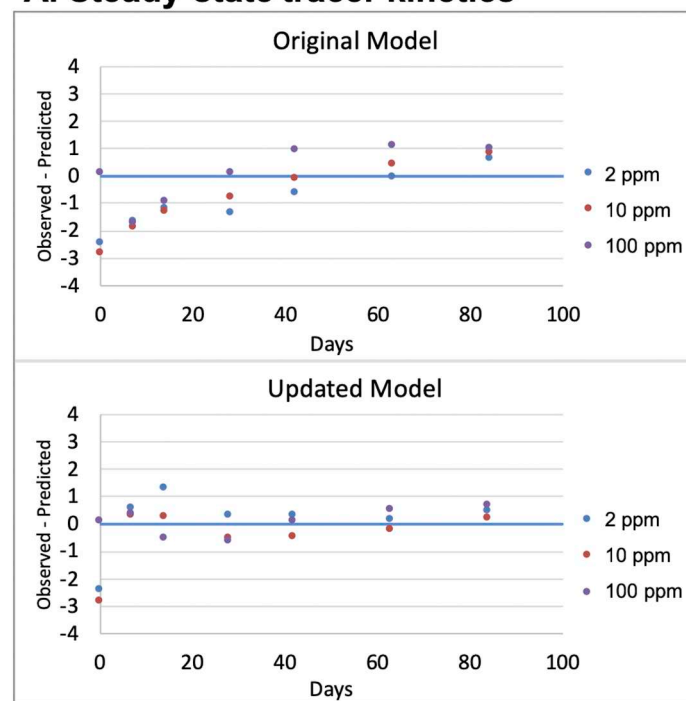
**Fig. 3.** 14 day inhalation tracer kinetics. Symbols represent the mean  $\pm$  SD from the data by [Dorman et al. \(2001b\)](#), whereas the lines in corresponding colors represent model simulations using the published (A) or updated (B) model for  $^{54}\text{Mn}$  tracer kinetics following a 14-d inhalation exposure at 0, 0.03, 0.3, or 3 mg Mn/ $\text{m}^3$ . The rats were fed on an approximately 125 ppm Mn diet prior to and during the 14-d inhalation exposure.

#### 4. Discussion

Previously published PBPK models were developed based on the available knowledge of the biological determinants of the uptake, distribution, and clearance for Mn and included aspects of the factors important for the distribution of Mn as they were known at the time of model development ([Nong et al., 2008](#); [Schroeter et al., 2011](#); [Yoon et al., 2011](#)). Because of the limitations in the understanding of the biological steps involved in essential metal homeostasis, the parameters of these PBPK models did not necessarily have a one-to-one correspondence to specific biological and/or biochemical processes in Mn homeostasis and disposition in the body. In particular, the mechanism of cellular transport and utilization in different tissues under various

exposure conditions had not been fully characterized when those models were being developed and when the structure of the initial models were finalized. As such, the primary goal in developing the previously published PBPK models was to have a model structure that captured the dose-dependent kinetics of Mn observed in rodents and, indirectly, provided confidence in utilizing a similar model structure for humans. Although the original model structure and parameters were based on particular assumptions about processes controlling Mn within tissues, they still allowed coherent integration of the known Mn biology at the time of model development, recapitulating the observed tissue Mn concentrations in various tissues within the body under various exposure conditions, and accounting for exposures that would lead to tissue overload and rapid increases in free Mn in tissues.

#### A. Steady-state tracer kinetics



#### B. 14 day inhalation tracer kinetics

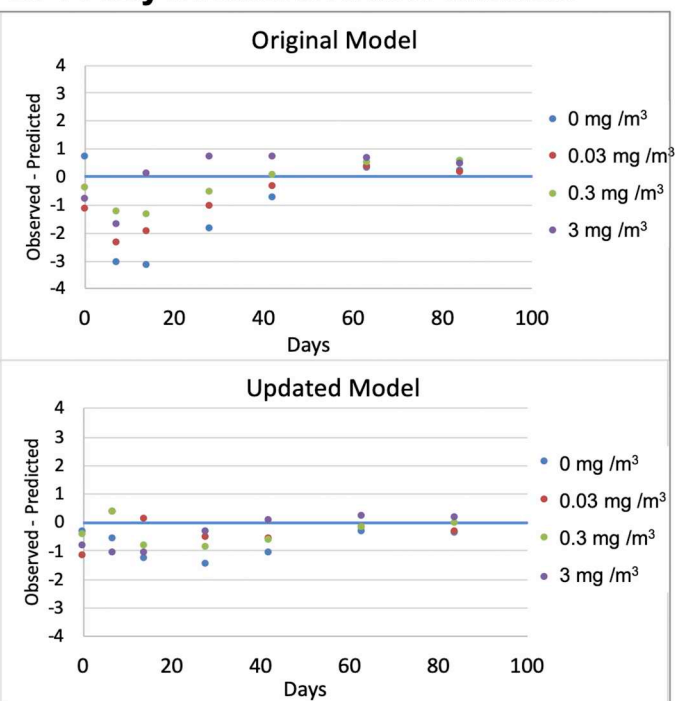


**Fig. 4.** Residual plots of the steady-state and 14 day inhalation tracer Mn kinetics. Residuals were calculated as the difference between the mean of the observed and predicted tracer levels at each time point reported in [Figs. 2 and 3](#). Residual plots show that the updated model provides a somewhat better description of the time-course of the experimental data than the original model. The updated model also provides a higher likelihood than the original model (data not shown).

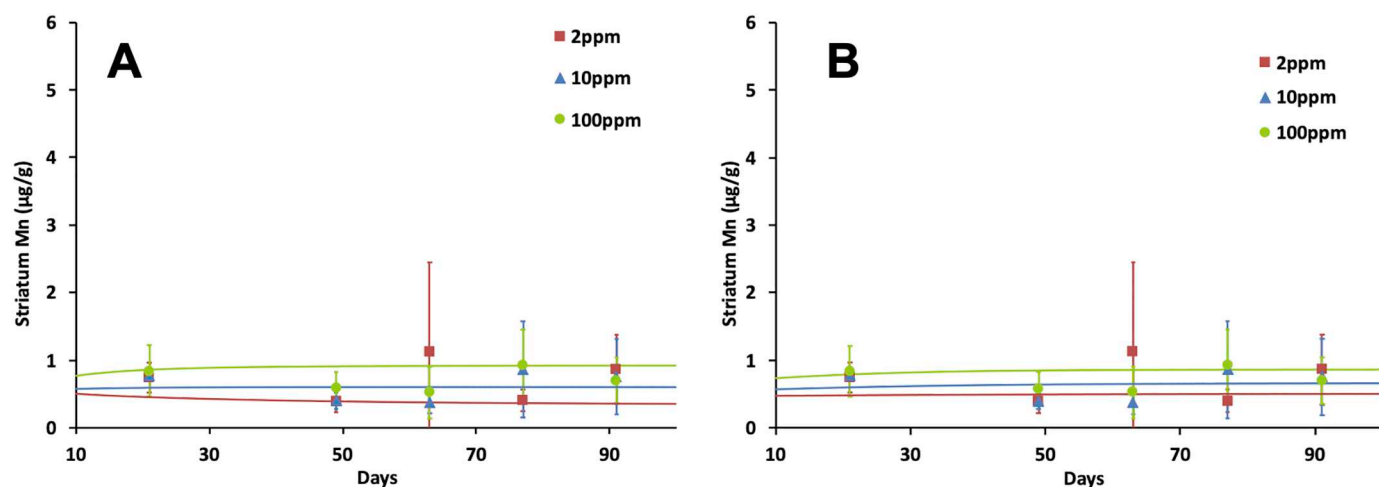


**Fig. 5.** A. Steady state brain striatum Mn concentration. Symbols represent the mean  $\pm$  SD calculated from the data reported by [Dorman et al. \(2001b\)](#), whereas the lines represent model simulations using the published (A) or updated (B) model for striatum Mn concentrations in rats fed on 2, 10 or 100 ppm Mn diet for 13 weeks reported in the same study. Fig. 5B. 14 day inhalation brain striatum Mn concentration. Symbols represent the mean  $\pm$  SD of the data reported by [Dorman et al. \(2001a\)](#), whereas the lines represent model simulations using the published (A) or updated (B) model for striatum Mn concentrations in rats exposed to 0.03, 0.3 and 3 mg Mn/m<sup>3</sup> for 6 h/d for 14 consecutive days ([Dorman et al., 2001a](#)). Steady state conditions are achieved more quickly in the updated model. Fig. 5C. 90 day inhalation striatum Mn concentration. Symbols represent the mean  $\pm$  SD of the data reported by [Dorman et al. \(2004\)](#), whereas the lines represent model simulations using the published (A & C) or updated (B & D) model for striatum Mn concentrations in rats during and following a 90-d inhalation exposure at 0.1 and 0.5 mg Mn/m<sup>3</sup>. The rats were fed on a 10 ppm diet from 30 d prior to exposure, and then they were exposed for 13 weeks for 6 h/d, 5 d/week with weekends off.

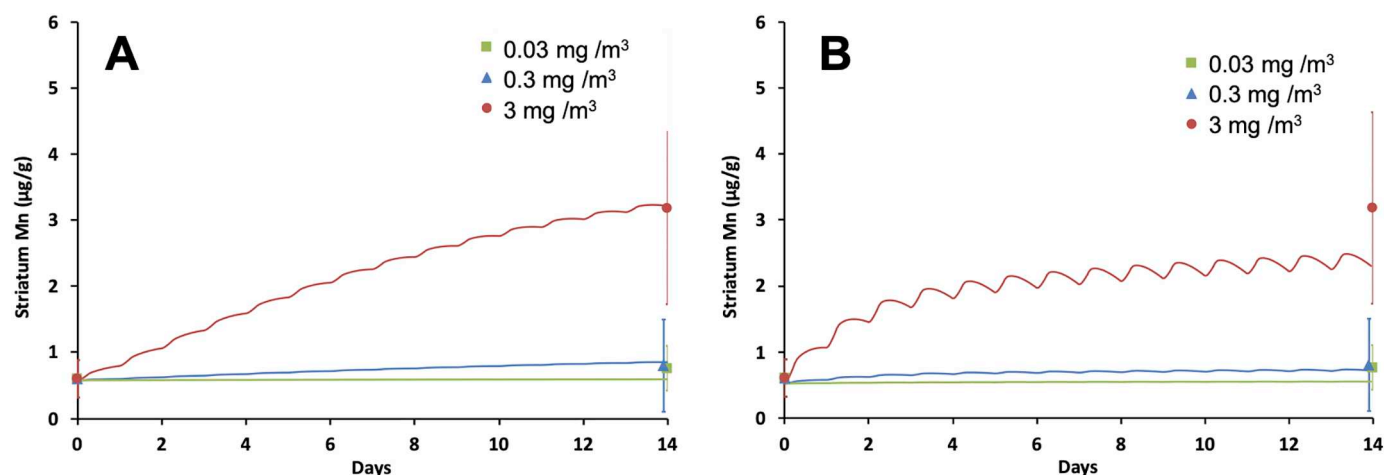


**Fig. 5.** (continued)

In both the original and this updated model structure, Mn time profiles in striatum after inhalation are predominantly determined by the increase in free Mn. As the free Mn, i.e., the form of Mn that is not associated with cellular macromolecules, is assumed to be responsible for Mn toxicity, this indicates that the predicted dose-response relationships from the two models would be similar. The processes accounting for the increase in free Mn with increasing tissue Mn differ in the original and this updated model. In the original models, slow dissociation rate constants provided the rate determining process for allowing Mn to exit the tissue. In this rapid equilibration model, the exchange between bound and free forms is rapid, and efflux rates from the tissues determine the rate at which free Mn leaves the tissues.

In the updated model, the KD values are similar among different tissues and consistent with similar utilization patterns for cellular Mn regardless of the tissue types. Differing amounts of Mn in various tissues -i.e., different levels of Mn containing macromolecules, lead to different background tissue Mn capacities in both models. While the KD in our updated model reflects a general binding affinity of multiple Mn-binding sites in tissues, there is little direct information about the amounts or affinity of these binding partners. Some experimental

studies reported the cellular free Mn in rat hepatocytes at around 0.2 to 1 µM using the electron paramagnetic resonance analysis technique ([Ash and Schramm, 1982](#); [Powell and Brew, 1976](#)). In addition, a few experimental studies reported dissociation constants for Mn binding/association to cellular macromolecules such as galactosyltransferase and Mn<sup>2+</sup>-ATPase in a low micromolar range ([Grisham and Mildvan, 1974](#); [Powell and Brew, 1976](#)). These estimates are in line with the physiological cellular concentration of free Mn and consistent with the KD we selected for our simulations.

Kinetics of Mn tracer in the whole body can be viewed as a reflection of free Mn behaviors under given exposure conditions, e.g., in the current study they were steady-state dietary or the end of inhalation exposure. Mn tracers are incorporated into cellular macromolecules, i.e., bound, and then released from those binding sites into the free form in the cell and subsequently exit the cells to blood for excretion to bile. The improvement with the updated model in providing better correspondence with tracer kinetics compared to the original model shows that the transients after changing exposure conditions need to be more rapid than allowed in the earlier description. The updated description also better captured the rapid clearance of circulating free Mn from



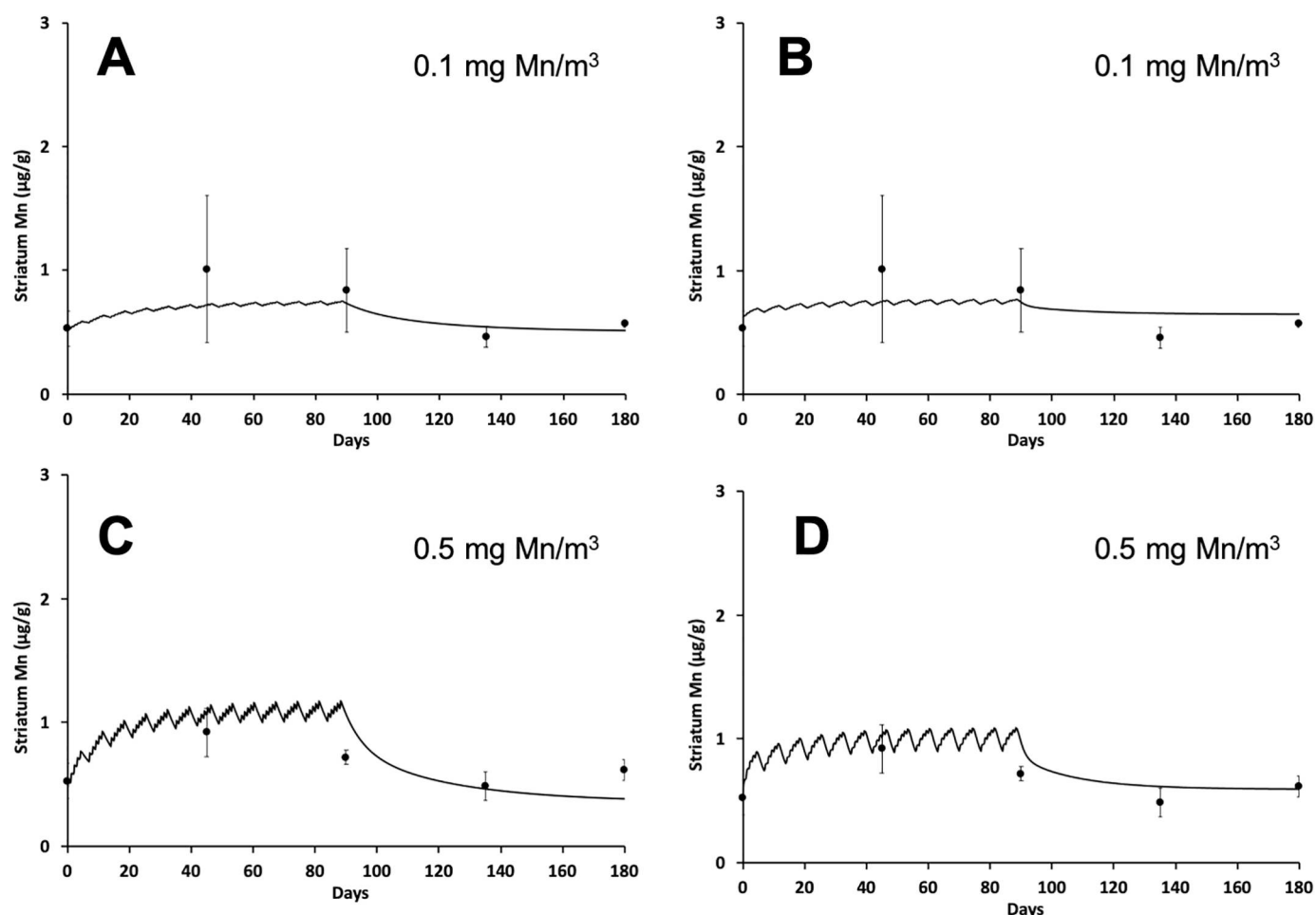


Fig. 5. (continued)

blood resulting from inhalation exposure, producing a more rapid rise in striatum Mn along with a greater daily fluctuation of total Mn in its time profile as well as a rapid return to the basal level at the cessation of the inhalation. Indeed, the updated model recapitulated the Mn elimination kinetics with changes in Mn intake much better than had been done previously.

The clear improvement in capturing Mn-transients, although either

model recapitulates longer-exposure tissue dose-response, indicates that the updated tissue description may be particularly useful in investigating mechanisms of Mn toxicity in cell culture models and non-mammalian systems such as zebrafish or *C. elegans*. PK models can be used in these situations to describe Mn kinetics in the culture system itself, cellular loading and unloading of Mn from and to the media, which can then facilitate the extrapolation of in vitro mechanistic

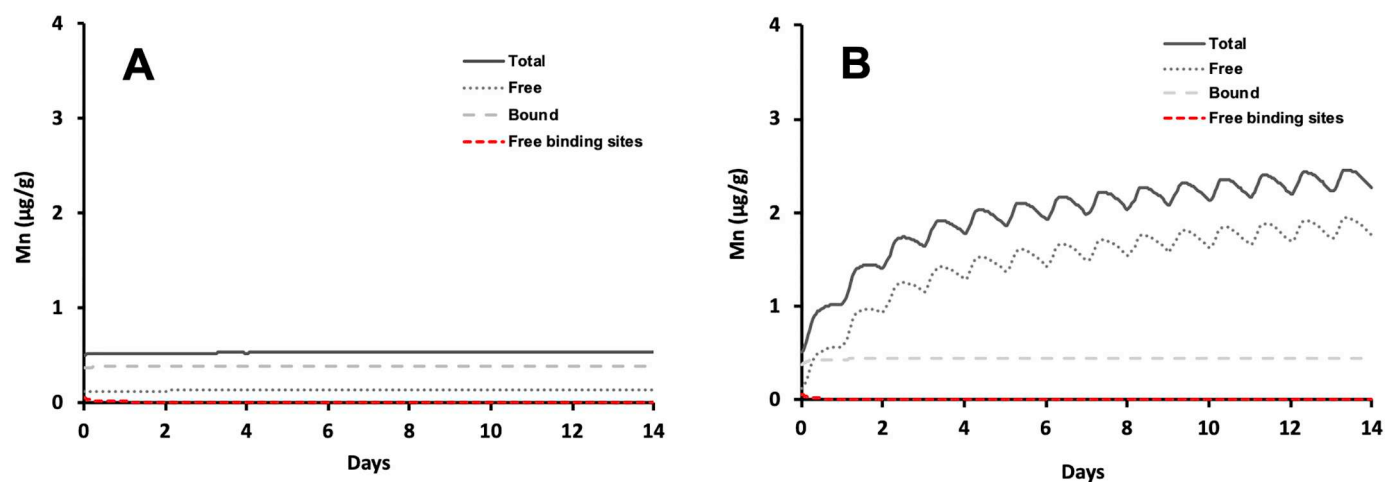


Fig. 6. Simulated brain striatum free and bound Mn kinetics. Striatum Mn kinetics in free vs. bound forms along with the remaining free binding site capacity were simulated using the updated model for the low concentration of 0.3 mg Mn/m<sup>3</sup> (A) and at high concentration of 3.0 mg Mn/m<sup>3</sup> (B) air Mn exposure for a 14-day period (Dorman et al., 2001a).

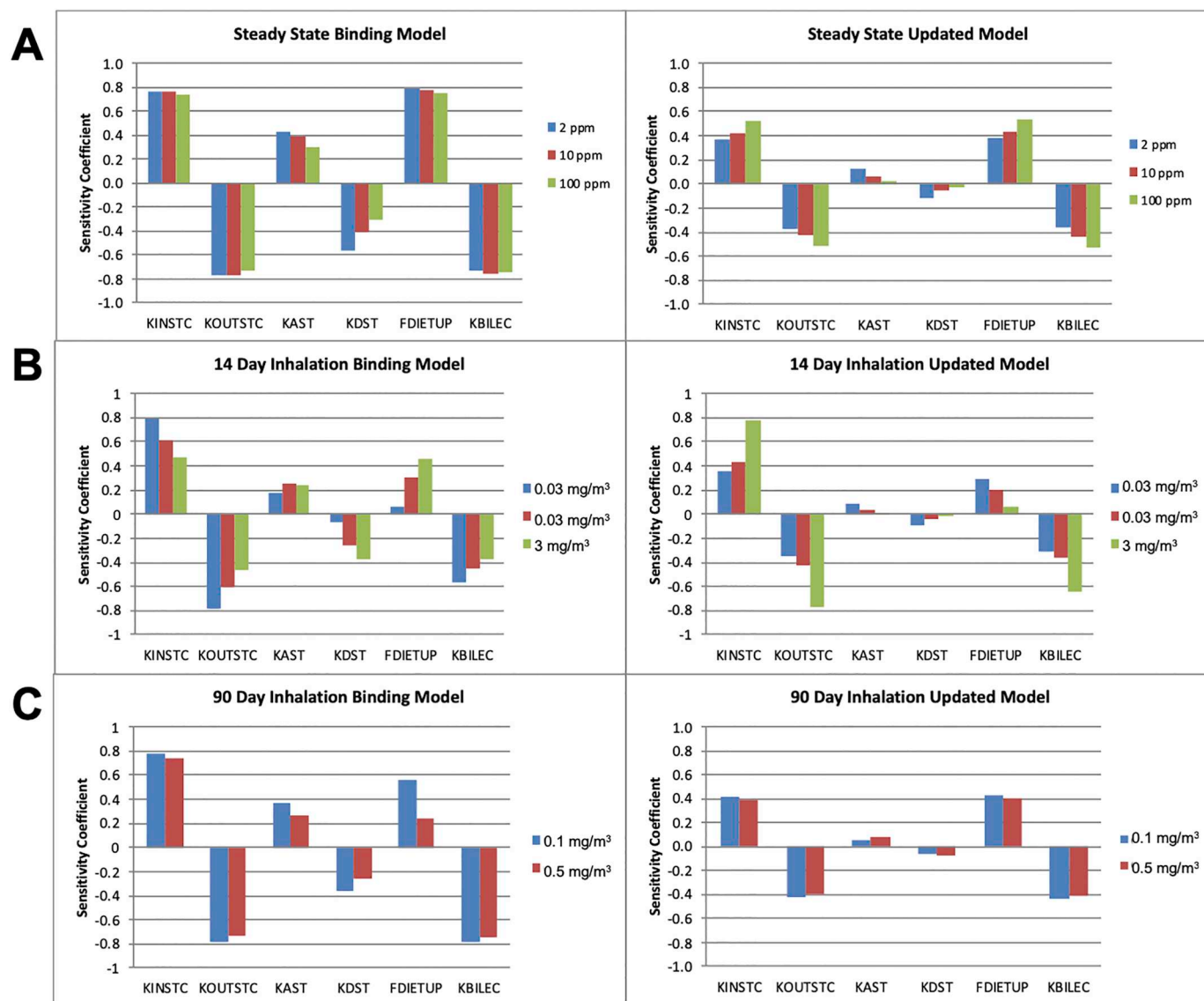


**Fig. 7.** Determinants of striatum Mn – comparison between the original vs. updated models. Sensitivity analysis was performed for 6 key parameters to test how sensitive the brain striatum Mn concentration is in response to a small change in each of these parameters. The resulting sensitivity coefficients are plotted here. Abbreviations for those 6 parameters are influx and efflux rates into and out of the striatum (KINSTC and KOUTSTC), association and dissociation rate constants in the striatum (KAST and KDST), the biliary excretion rate constant (KBILEC), and the absorption fraction in the gut (FDIETUP).

findings and dose-response relationships to corresponding in vivo conditions. For example, the new Mn model could provide a useful insight into the intracellular trafficking and efflux of Mn leading to better understanding of the concentration-dependent control of Mn transports via metal transporters at cellular surfaces as well as the intracellular movement of Mn in relation with cellular toxicity in in vitro models such as primary neuronal cells and model organisms such as *C. elegans* (Leyva-Illades et al., 2014; Lin et al., 2017).

With the rapid association/dissociation rates in this updated model, it was no longer necessary to include induction of the biliary excretion rate constant as body burdens of Mn increased (Fig. S1). The simulated dose-dependent rate of, or amount of, Mn excretion by the updated model remained comparable to that simulated by the original model indicating that in the new description, free Mn-dependent biliary excretion alone is sufficient to describe dose-dependent changes in Mn excretion via bile. This difference occurs because in the updated model, the saturation of binding sites throughout the body and more rapid increases in blood Mn drive the rate of biliary excretion rather than requiring enhancement of the rate constant to effectively provide a

draw on tissue Mn in the face of the slow dissociation constant for tissue stores of Mn.

For the published models, the tissue binding and cellular transport parameters for rat striatum were allometrically scaled to monkey globus pallidus together with further optimization based on the available tissue time course data in monkeys (Nong et al., 2008; Schroeter et al., 2011). Inter-species extrapolation of the monkey pallidal parameters to those in humans was also based on the allometrical scaling along with the available human data (Schroeter et al., 2011; Yoon et al., 2011). Currently, we are investigating the feasibility of updating the monkey model with the rapid binding assumption as described in this study. Once successfully evaluated, inter-species extrapolation of the updated monkey model to human can be performed in a similar manner to the published models.

Since the motivation for recasting the Nong et al. (2008) model structure to this rapid association-dissociation model was the increasing appreciation of transporters in controlling metal kinetics and tissue accumulation, it is of interest to consider recent work on Mn-metal transporters and Mn toxicity in mice. Over the past two years research

has appeared evaluating the role of two Mn efflux transporters, SLC39A14 and SLC30A10. The work with both transporters used transgenic mice. With SLC39A14 (Xin et al., 2017), wild-type, whole body knock out (KO) and hepatocyte specific KOs were evaluated. For similar Mn intakes, the whole-body KO mice had 20 to 30-fold increases in blood and brain Mn compared to WT-mice. With the liver specific KOs, except for relatively small increase in liver itself, there was little change in Mn in other tissues. The study with SLC39A14 also evaluated the effect of the KO on other transporters, finding modest changes in another Mn-efflux transporter, SLC30A10, in several tissues.

A more extensive evaluation was reported with SLC30A10 (Taylor et al., 2019) using 5 strains of mice: WT, whole body KO, hepatocyte KO, endoderm specific KOs (i.e., KOs in both the liver and GI-tract), and pan-neuronal/glia KO. Whole body KOs increased brain Mn by about 20-fold and blood Mn by 20- to 25-fold. As with SLC39A14, liver specific KOs caused only small changes in blood and brain Mn. The endoderm specific KOs had increases in blood and brain Mn nearly as great as those seen in whole body KO mice. Surprisingly, the pan-neuronal/glia KOs had minimal increases in brain Mn compared to WT-mice.

The appearance of these new data sets on differential tissue Mn accumulation with manipulation of specific transporters represents an opportunity to further develop our restructured model with more explicit inclusion of transporter tissue distribution. As has been the practice with many other PBPK modeling programs, the ability to include different structural characteristics within models, in this case, different distributions and activities of transporters, together with different model structures, such as this rapid association-dissociation model, should provide important quantitative tests to what might remain qualitative conclusions about the influence of different tissue distributions of transporters on tissue accumulation of Mn.

Some of the observations with tissue specific KO mice are consistent with prior work from the nutritional literature on regulation of uptake with changing diets. Teeguarden et al. (2007) examined the uptake of Mn with increasing dietary Mn showing that the rate constant for uptake, a measure of the ability of Mn to move to the enterocyte and out was reduced 23-fold going from dietary intake of 0.49 to 73 ppm, while the rate of biliary excretion increased only by a factor of 4 (data from Malecki et al., 1996). These changes and other work showed that uptake from the gut to the circulation was under tight control. These processes indicated a primary role of enterocyte elimination of Mn in controlling the proportion retained from the diet rather than the biliary excretion after absorption. Clearly, the primacy of enterocyte function in controlling Mn homeostasis is also evident from these liver specific transporter KO mice. The role of biliary excretion is to move Mn into bile where it also is sensed by enterocytes. The most intriguing observation is the lack of brain accumulation in the pan-neuronal/glia KO mice. This behavior might indicate a role for SLC30A10 in intake as well as efflux at higher blood Mn or the presence of coordinate effects on expression of other efflux transporters in the SLC30A10 KO mice.

Our modeling efforts over the past decade have focused on uptake and distribution of Mn after inhalation exposures with animals or humans (Yoon et al., 2014). With inhalation, and uptake of Mn from the lungs, the control of uptake by enterocytes primarily affects the proportion Mn retained from the diet with the liver moving Mn from blood to the intestinal lumen. The increasing knowledge of tissue distribution and function in these transgenic mice coupled with species-specific PBPK modeling should be useful for informing risk assessments for both oral and inhalation exposures.

It also bears some emphasis that this recast rapid-association-dissociation PBPK model can be easily adapted to account for transporter distribution and for the characteristics of kinetic parameters of transporters in diverse tissues as such data become available. These models, as with those derived from the older model architecture, are also readily amenable to inclusion of life stage changes in the concentrations of transporters in animals and humans and for different life stages (Yoon et al., 2014).

## 5. Conclusion

Our alternative parameterization in an updated PBPK model successfully describes Mn kinetics in tissues in adult rats exposed to Mn both in their diet and by inhalation. The model structure with rapid binding was better in capturing transient dose dependent elimination processes of the tracer as dosing patterns and dose levels changed. However, the two model structures – with different kinetics of tissue binding – both capture the dose-dependent and tissue-specific kinetic behavior of Mn in adult rats for longer-term exposure conditions. The equivalent performance of the published and updated models in capturing the non-linear kinetics of Mn provides greater confidence in using the previously published Mn PBPK models in risk assessment, as updating the other published Mn models to incorporate the alternative parameterization is unlikely to lead to materially different outcomes when modeling changes in Mn concentration under different exposure conditions once steady-state is reached. The updated model has promise for extending the application of the Mn PBPK model to develop studies on mechanism-based toxicity testing approaches, in particular focusing on the target brain regions of mid-brain for Mn neurotoxicity such as striatum and globus pallidus (Aschner et al., 2005; Dorman et al., 2000), incorporate those new data on Mn transporters from non-animal and other emerging alternative models to the PBPK models for in vitro to in vivo extrapolation, and study periods of rapid changes in Mn exposures in various populations. Such abilities will also contribute to adding weight of evidence increasing confidence in model-based risk assessment.

## Transparency document

The Transparency document associated to this article can be found, in the online version

## Acknowledgements

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.taap.2019.04.006>.

## References

- Andersen, M.E., Dorman, D.C., Clewell III, H.J., Taylor, M.D., Nong, A., 2010. Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment. *J. Toxic. Environ. Health A* 73 (2–3), 217–234.
- Aschner, M., Erikson, K., 2017. Manganese. *Adv. Nutr.* 8, 520–521. <https://doi.org/10.3945/an.117.015305>.
- Aschner, M., Erikson, K.M., Dorman, D.C., 2005. Manganese dosimetry: species differences and implications for neurotoxicity. *Crit. Rev. Toxicol.* 35 (1), 1–32.
- Aschner, M., Guilarte, T.R., Schneider, J.S., Zheng, W., 2007. Manganese: recent advances in understanding its transport and neurotoxicity. *Toxicol. Appl. Pharmacol.* 221 (2), 131–147.
- Ash, D.E., Schramm, V.L., 1982. Determination of free and bound manganese(II) in hepatocytes from fed and fasted rats. *J. Biol. Chem.* 257, 9261–9264.
- ATSDR, 2013. Toxicological Profile for Manganese. U. S. Dep. Heal. Hum. Serv. <https://doi.org/10.1155/2013/286524>.
- Chen, P., Chakraborty, S., Mukhopadhyay, S., Lee, E., Paoliello, M.M.B., Bowman, A.B., Aschner, M., 2015. Manganese homeostasis in the nervous system. *J. Neurochem.* 134, 601–610.
- Dorman, D.C., Struve, M.F., Vitarella, D., Byerly, F.L., Goetz, J., Miller, R., 2000. Neurotoxicity of manganese chloride in neonatal and adult CD rats following sub-chronic (21-day) high-dose oral exposure. *J. Appl. Toxicol.* 20 (3), 179–187.
- Dorman, D.C., Struve, M.F., James, R.A., McManus, B.E., Marshall, M.W., Wong, B.A., 2001a. Influence of dietary manganese on the pharmacokinetics of inhaled manganese sulfate in male CD rats. *Toxicol. Sci.* 60 (2), 242–251.
- Dorman, D.C., Struve, M.F., James, R.A., Marshall, M.W., Parkinson, C.U., Wong, B.A.,

- 2001b. Influence of particle solubility on the delivery of inhaled manganese to the rat brain: manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure. *Toxicol. Appl. Pharmacol.* 170 (2), 79–87.
- Dorman, D.C., McManus, B.E., Marshall, M.W., James, R.A., Struve, M.F., 2004. Old age and gender influence the pharmacokinetics of inhaled manganese sulfate and manganese phosphate in rats. *Toxicol. Appl. Pharmacol.* 197 (2), 113–124.
- Freeland-Graves, J., 1994. Derivation of manganese estimated safe and adequate daily dietary intakes. *Risk Assess. Essential Elements* 237–252.
- Grisham, C.M., Mildvan, A.S., 1974. Magnetic resonance and kinetic studies of the mechanism of sodium and potassium ion-activated adenosine triphosphatase. *J. Biol. Chem.* 249 (10), 3187–3197.
- Hutchens, S., Liu, C., Jursa, T., Shawlot, W., Chaffee, B.K., Yin, W., Gore, A.C., Aschner, M., Smith, D.R., Mukhopadhyay, S., 2017. Deficiency in the manganese efflux transporter SLC30A10 induces severe hypothyroidism in mice. *J. Biol. Chem. jbc-M117*.
- Leyva-Illades, D., Chen, P., Zogzas, C.E., Hutchens, S., Mercado, J.M., Swaim, C.D., Morrisett, R.A., Bowman, A.B., Aschner, M., Mukhopadhyay, S., 2014. SLC30A10 is a cell surface-localized manganese efflux transporter, and parkinsonism-causing mutations block its intracellular trafficking and efflux activity. *J. Neurosci.* 34 (42), 14079–14095.
- Lin, W., Vann, D.R., Doulias, P.T., Wang, T., Landesberg, G., Li, X., Ricciotti, E., Scalia, R., He, M., Hand, N.J., Rader, D.J., 2017. Hepatic metal ion transporter ZIP8 regulates manganese homeostasis and manganese-dependent enzyme activity. *J. Clin. Invest.* 127 (6), 2407–2417.
- Malecki, E.A., Radzanowski, G.M., Radzanowski, T.J., Gallaher, D.D., Greger, J.L., 1996. Biliary manganese excretion in conscious rats is affected by acute and chronic manganese intake but not by dietary fat. *J. Nutr.* 126 (2), 489–498.
- Nong, A., Taylor, M.D., Clewell III, H.J., Dorman, D.C., Andersen, M.E., 2009 Mar. Manganese tissue dosimetry in rats and monkeys: accounting for dietary and inhaled Mn with physiologically based pharmacokinetic modeling. *Toxicol. Sci.* 108 (1), 22–34. <https://doi.org/10.1093/toxsci/kfn264>.
- Nong, A., Teeguarden, J.G., Clewell III, H.J., Dorman, D.C., Andersen, M.E., 2008. Pharmacokinetic modeling of manganese in the rat IV: assessing factors that contribute to brain accumulation during inhalation exposure. *J. Toxic. Environ. Health A* 71 (7), 413–426.
- Powell, J.T., Brew, K., 1976. Metal ion activation of galactosyltransferase. *J. Biol. Chem.* 251 (12), 3645–3652.
- Roels, H.A., Ortega Eslava, M.I., Ceulemans, E., Robert, A., Lison, D., 1999. Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. *Neurotoxicology* 20, 255–271.
- Santos, D., Batoreu, C., Mateus, L., Marreilha dos Santos, A.P., Aschner, M., 2014. Manganese in human parenteral nutrition: considerations for toxicity and biomonitoring. *Neurotoxicology* 43, 36–45.
- Schroeter, J.D., Nong, A., Yoon, M., Taylor, M.D., Dorman, D.C., Andersen, M.E., Clewell 3rd, H.J., 2011. Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multi-route physiologically based pharmacokinetic models. *Toxicol. Sci.* 120, 481–498.
- Taylor, C.A., Hutchens, S., Liu, C., Jursa, T., Shawlot, W., Aschner, M., Smith, D.R., Mukhopadhyay, S., 2019. SLC30A10 transporter in the digestive system regulates brain manganese under basal conditions while brain SLC30A10 protects against neurotoxicity. *J. Biol. Chem.* 294 (6), 1860–1876.
- Teeguarden, J.G., Dorman, D.C., Covington, T.R., Clewell III, H.J., Andersen, M.E., 2007. Pharmacokinetic modeling of manganese. I. Dose dependencies of uptake and elimination. *J. Toxic. Environ. Health A* 70 (18), 1493–1504.
- Tuschl, K., Meyer, E., Valdivia, L.E., Zhao, N., Dadswell, C., Abdul-Sada, A., Hung, C.Y., Simpson, M.A., Chong, W.K., Jacques, T.S., Woltjer, R.L., 2016. Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. *Nat. Commun.* 7, 11601.
- Xin, Y., Gao, H., Wang, J., Qiang, Y., Imam, M.U., Li, Y., Wang, J., Zhang, R., Zhang, H., Yu, Y., Wang, H., 2017. Manganese transporter Slc39a14 deficiency revealed its key role in maintaining manganese homeostasis in mice. *Cell Discov.* 3, 17025.
- Yoon, M., Schroeter, J.D., Nong, A., Taylor, M.D., Dorman, D.C., Andersen, M.E., Clewell III, H.J., 2011. Physiologically based pharmacokinetic modeling of fetal and neonatal manganese exposure in humans: describing manganese homeostasis during development. *Toxicol. Sci.* 122 (2), 297–316.
- Yoon, M., Taylor, M.D., Clewell, H.J., Andersen, M.E., 2014. Modeling manganese kinetics for human health risk assessment. In: *Manganese in Health and Disease*. Royal Society of Chemistry, pp. 322–354.



# Incorporation of rapid association/dissociation processes in tissues into the monkey and human physiologically based pharmacokinetic models for manganese

AUTHORS

Jerry Campbell<sup>1</sup>, Harvey Clewell<sup>1</sup>, Cynthia VanLandingham<sup>2</sup>, Robinan Gentry<sup>2</sup>, Athena Keene<sup>3</sup>, Michael Taylor<sup>4</sup>, and Mel Andersen<sup>5</sup>

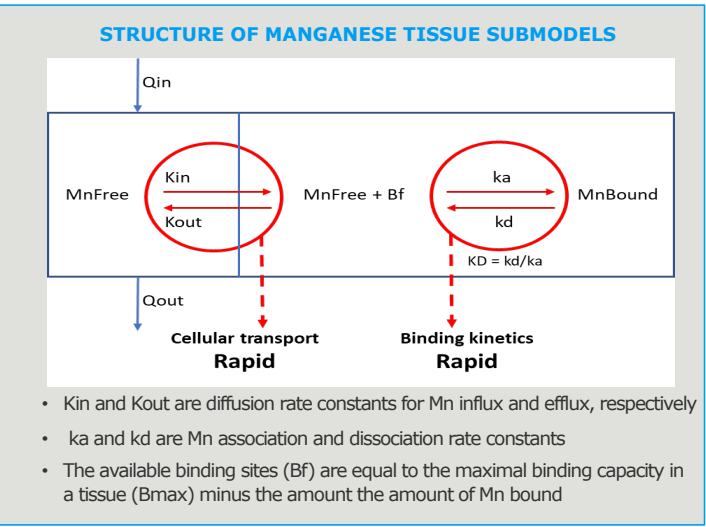
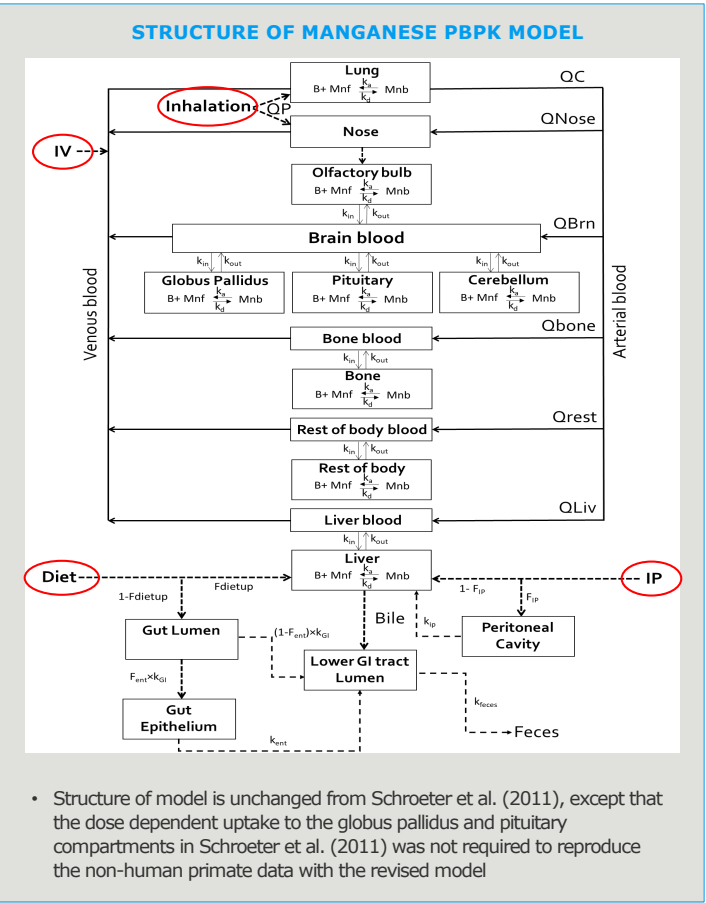
<sup>1</sup>Ramboll, RTP, NC  
<sup>2</sup>Ramboll, Monroe, LA  
<sup>3</sup>Afton Chemical Corporation, Richmond, VA  
<sup>4</sup>NIPERA, Durham, NC  
<sup>5</sup>Andersen ToxConsulting LLC, Denver, NC

ABSTRACT

In published physiologically based pharmacokinetic (PBPK) models for manganese (Mn), the kinetics of transport of Mn to and from tissues was primarily driven by Mn binding in tissues. In subsequent years, appreciation of the role of cellular membrane transporters in the homeostasis of Mn has grown appreciably. Based on these insights, an updated Mn model for primates, following similar work with rats, was developed that accounts for more rapid rates of transporter-mediated entry into tissues, interaction of Mn with cellular binding sites and accumulation of free Mn in tissues after saturation of these Mn-binding sites. This alternative structure successfully described Mn kinetics in tissues in non-human primates and humans exposed to Mn via various routes including diet, oral gavage, inhalation, and intraperitoneal, subcutaneous, or intravenous injection. An important contribution of this effort is showing that the extension of the rate constants for cellular transport and intracellular disposition of Mn established in the monkey were also able to describe kinetic data from humans. The increased biological relevance of the Mn model structure and parameters provides greater confidence in applying the Mn PBPK models to risk assessment. This model is also well-suited to extension to explicitly incorporate emerging information on the role of transporters in tissue disposition, intestinal uptake, and hepatobiliary excretion of Mn.

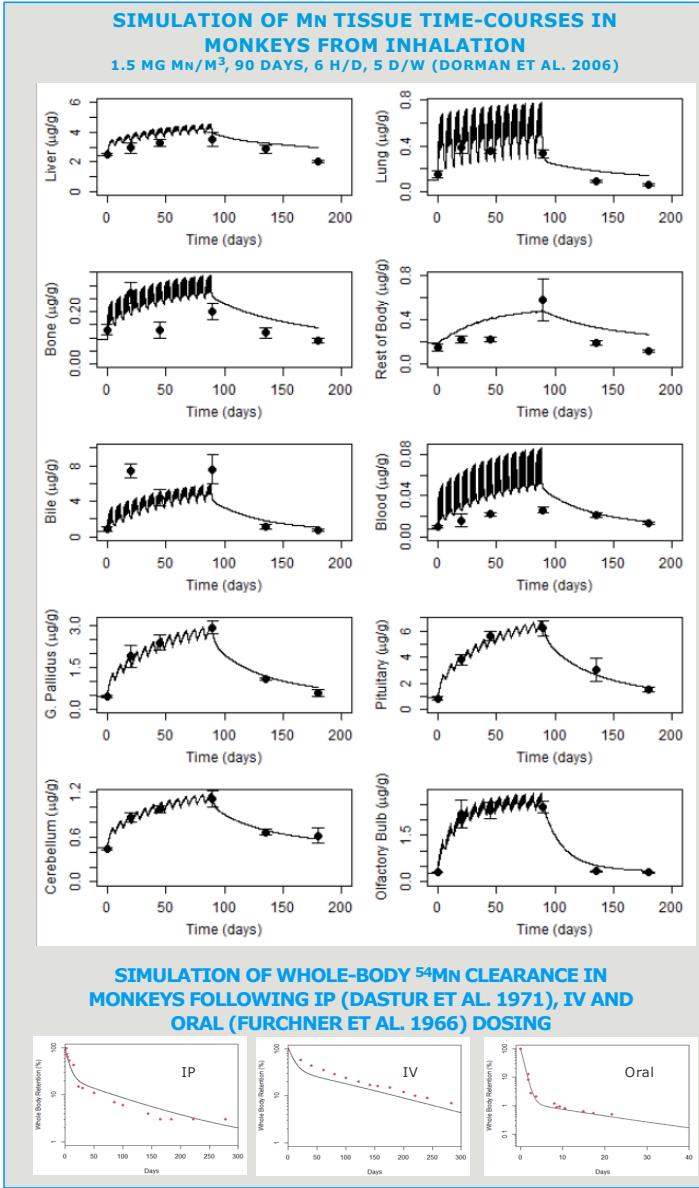
BACKGROUND

- Early Mn compartmental PK models were unable to capture the rapid rise in tissue Mn concentrations seen during inhalation exposure to high Mn concentrations, due to their reliance on linear first-order processes to simulate Mn tissue kinetics under both normal and deficient dietary conditions. Subsequently, a successful PBPK model structure was developed in the rat, monkey and human that included saturable Mn tissue stores (Nong et al., 2009; Schroeter et al. 2011).
- Since the publication of these models, further investigation of the processes important to metal homeostasis has indicated that uptake into and efflux out of tissues are due to actions of cellular membrane transporters and less avid, more readily reversible binding of Mn within tissues (Aschner and Erikson, 2017; Chen et al., 2015).
- Solute transporter proteins recently identified to be involved in Mn homeostasis in vertebrates include SLC30A10, SLC39A8 and SLC39A14 (Mercadante et al., 2019; Park et al. 2015; Tuschl et al., 2016).
- In light of these findings, Yoon et al. (2019) recast the published PBPK model for the adult rat (Nong et al., 2009) to have more rapid tissue uptake and more rapid binding and association of Mn with binding sites in tissues.
- In the current study, the same model structure with more rapid association-dissociation processes for Mn binding in tissues was incorporated into the non-human primate and human Mn PBPK model (Schroeter et al. 2011), based on the current understanding of the role of transporters in the influx and efflux of Mn.

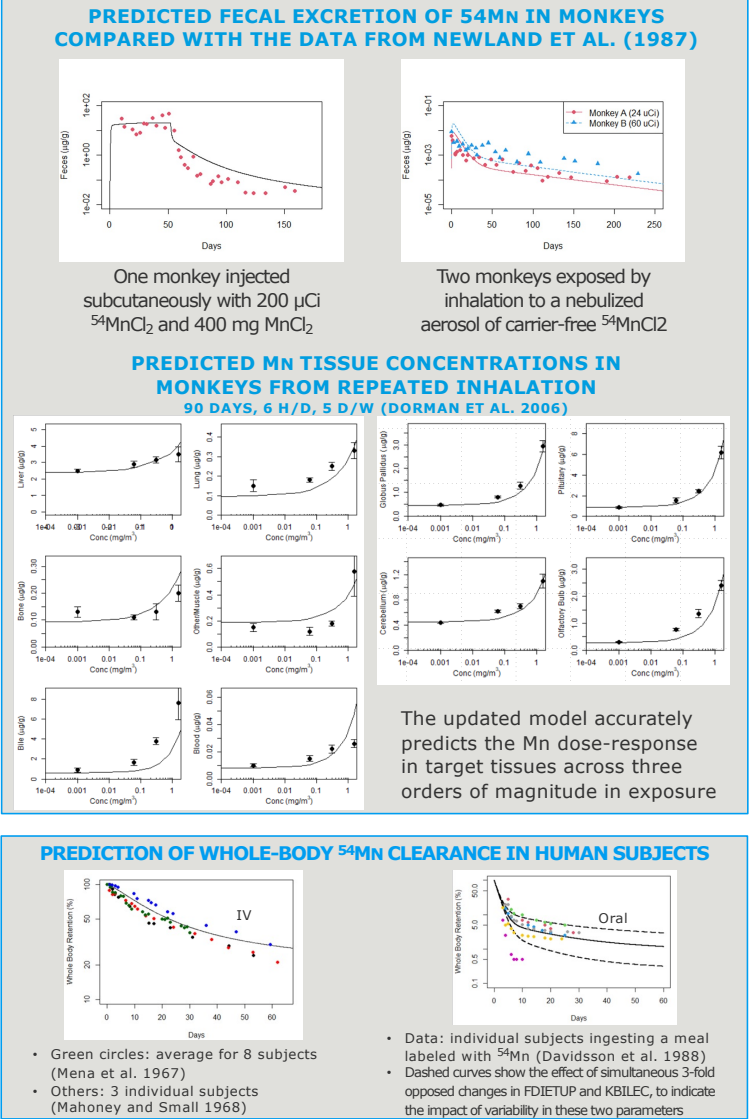


MODEL PARAMETERIZATION

- Mn tissue binding ( $k_a$  and  $k_d$ ) constants were retained from rat model.
- Parameter optimization for the monkey Mn transporter model was conducted to simultaneously estimate three parameters ( $k_{in}$ ,  $k_{out}$  and  $B_{max}$ ) for each tissue.
- The datasets used for optimization included the Dorman et al. (2006a) baseline diet values and 1.5 mg/m<sup>3</sup> inhalation time-course data and the whole-body clearance of <sup>54</sup>Mn: IP (Dastur et al. 1971), IV and oral (Furchner et al. 1966) (below).
- Apart from physiological parameters, other human parameters were scaled allometrically from the monkey.



MODEL VALIDATION



CONCLUSIONS

- PBPK models with more loosely bound tissue Mn better represent the known biochemistry of Mn compared to earlier models with much more tightly bound, slowly exchangeable Mn.
- Despite the improved fidelity with Mn biology in the new model, both the older and newer PBPK models adequately describe the dose dependence of Mn concentration in various brain regions with increasing inhalation exposures or dietary intakes to support risk assessments of manganese exposure.

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CONTACT: Jerry Campbell (jcampbell@ramboll.com)

**Appendix O: DEQ and OHA Framing  
Document for DEQ's ATSAC: Petition  
for Changes to DEQ's Manganese  
Toxicity Reference Value for Acute  
Exposure**



Oregon Department of Environmental Quality

# Framing Document for DEQ's Air Toxics Science Advisory Committee

## Petition for Changes to DEQ's Manganese Toxicity Reference Value for Acute Exposure

### Overview

The Oregon Department of Environmental Quality (DEQ) and Oregon Health Authority (OHA) are currently reviewing the inhalation toxicity reference values (TRVs) used in DEQ's air quality programs. Existing TRVs are in Oregon Administrative Rule (OAR, [340-247-8010 Table 2](#)). As part of the TRV review process, DEQ OARs give an option for members of the public to [submit petitions](#) to suggest TRV updates. DEQ welcomed petitions for consideration during the current TRV update process. Petitions were due in late 2022.

DEQ received one petition to change DEQ's TRV for acute exposure (24-hour) to manganese (Bridgewater Group, 2022). Hereafter, this TRV is referred to as the **"acute TRV"**. This petition was prepared by Bridgewater Group, a consulting firm that works extensively with sources in Oregon on air quality permitting actions, including Cleaner Air Oregon Risk Assessments. The toxicological information and analysis for the petition was provided by ToxStrategies, a scientific consulting firm that provides information to address regulatory issues. The petition proposes to increase the DEQ acute manganese TRV from  $0.3 \mu\text{g}/\text{m}^3$  to  $5 \mu\text{g}/\text{m}^3$ , which is consistent with the 24-hour ambient monitoring comparison value developed by the Texas Commission of Environmental Quality (TCEQ, 2017). While the TRV proposed in the petition is equivalent to the TCEQ TRV, the petition proposes a slightly different set of uncertainty factors (UFs) than the ones used by TCEQ, which are discussed in detail further in this document.

Staff at ToxStrategies also published a peer-reviewed manuscript titled "Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese" in *Regulatory Toxicology and Pharmacology* (Perry et al., 2023); hereafter, referred to as **"Perry et al."**. This manuscript states that the work was supported by Gunderson, LLC, of Portland, OR and Cascade Steel Rolling Mills, Inc, of McMinnville, OR. The manganese acute TRV proposed in Perry et al. is also equivalent to the TCEQ TRV and petition TRV; however, Perry et al. proposes yet another slightly different set of uncertainty factors than the ones used by TCEQ and the petition, which are discussed in detail further in this document.

DEQ is seeking feedback from ATSAC on this petition. DEQ does not have a final proposal yet for changes to DEQ's acute manganese TRV. ATSAC member feedback will inform DEQ's proposal. This framing document provides summary information for ATSAC members to prepare for a discussion and includes key questions that DEQ will ask ATSAC members at the next ATSAC meeting.

### DEQ's Request for ATSAC Members

- 1) Read the petition DEQ received for the acute manganese TRV ([link](#)).
- 2) Read Perry et al. 2023 "Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese" ([link](#)).
- 3) Read this framing document for DEQ's initial thoughts on and questions about the petition. This framing document is meant to be supplemental to the petition, so it does not summarize all the background information that the petition includes.
- 4) Prepare answers to the questions at the end of this framing document, which we will discuss at our next ATSAC meeting. Kearns & West will reach out soon to schedule a meeting.

### Translation or other formats

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Here are supplemental documents that may help you prepare for the discussion. Please note that the petition includes its own supplemental information as appendices (e.g., Dorman et al. 2005).

- [TCEQ Guidelines to Develop Toxicity Factors](#) (TCEQ, 2015)
- [TCEQ Developmental Support Document on Manganese and Inorganic Manganese Compounds](#) (TCEQ, 2017)
- [California's Office of Environmental Health Hazard Assessment \(OEHHA\) Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries: Manganese and Compounds Reference Exposure Levels](#), starts on page 434 (OEHHA, 2008b)

If you have additional information that you would like other ATSAC members to consider, please submit it to DEQ well in advance of the ATSAC meeting so that others have sufficient time to review.

## TRV Background

As a reminder, DEQ uses the term TRV when referring to similarly derived health-based toxicity values developed by other agencies. Additional background information on TRVs and the TRV update process can be found in these fact sheets: [Proposed TRV Update and Selection Process for ATSAC Review](#) and [Updates after the ATSAC Meeting](#). Oregon Administrative Rules (OARs), adopted by the Oregon Environmental Quality Commission (EQC), specify sources of toxicity information considered to be authoritative in terms of their scientific rigor and comprehensive methods for producing toxicity information ([OAR 340-247-0030](#)). Authoritative sources for acute exposure (24-hour) TRVs include the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) and California Environmental Protection Agency (CalEPA). DEQ in consultation with ATSAC can also propose an acute exposure TRV for the EQC to consider, which gives DEQ flexibility in choosing and setting acute TRVs that best match our 24-hour exposure duration definition.

## Changing DEQ's Prior Acute Value for Manganese

DEQ's existing manganese acute TRV is based on a chronic exposure TRV from CalEPA's Office of Environmental Health and Hazard Assessment (OEHHA). The critical study reported neurotoxicity in workers exposed to manganese for an average of 5.3 years and up to 17 years (Roels et al., 1992). In agreement with the petition, DEQ acknowledges that deriving acute TRVs from chronic TRVs is not ideal and, where appropriate and possible, DEQ would prefer to derive an acute TRV from a study with an acute exposure duration. DEQ states in the [TRV update fact sheet](#) that DEQ and OHA would prioritize finding alternative TRVs that are based on studies with short-term/acute exposure periods during its review of acute TRVs. The petition goes into detail on the lack of manganese acute TRVs available from DEQ's authoritative sources.

DEQ agrees that TCEQ's manganese acute TRV is a good resource because (1) TCEQ's acute TRVs match DEQ's acute exposure time (24 hours), (2) TCEQ's manganese acute TRV is based on short-term toxicity study data, and (3) TCEQ provides comprehensive developmental support documentation. The following pages of this framing document outline and compare the toxicity information used in TCEQ's developmental support document, the petition, and Perry et al. (2023).

As shown in Table 1, both TCEQ and the petition use the same critical study (Dorman et al., 2005). Perry et al. (2023) uses two critical studies (Dorman et al., 2005; Erikson et al., 2008). Perry et al. states "reversible bronchiolitis (Dorman et al., 2005) and biochemical markers of oxidative stress in the brain (decreased GSH and reversible increased GS protein with decreased gene expression) (Erikson et al., 2008) in monkeys, following 90 h of exposure, is considered the most relevant POD" (2023).



TCEQ, the petition, and Perry et al. all use the same point of departure (POD) value (Table 1).

**Table 1.** Information on the critical studies used in the TRVs for acute exposure to manganese.

|                                                | Critical Study Author and Year                               | Critical Study Species             | Critical Effect Target Organ | Description of TRV Critical Effect                                                                                                                                       | Duration of Exposure in Critical Study                | Point of Departure (POD) Method                            | POD Value (mg/m <sup>3</sup> ) |
|------------------------------------------------|--------------------------------------------------------------|------------------------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------|--------------------------------|
| Used in TCEQ, Petition, and Perry et al., 2023 | <b>Dorman et al. 2005</b>                                    | Male Rhesus Monkeys (20-24 months) | Respiratory System           | Inflammatory airway changes (e.g., mild bronchiolitis, alveolar duct inflammation)                                                                                       | 6 hrs/day, 5 days/week, 15 exposure days*             | Lowest observed adverse effects level (LOAEL) <sup>°</sup> | 1.5                            |
| Used in Perry et al., 2023                     | <b>Erikson et al. 2008</b> in addition to Dorman et al. 2005 | Male Rhesus Monkeys (20-24 months) | Nervous System               | Biochemical markers of oxidative stress in the brain (decreased glutathione levels and reversible increased glutamine synthetase protein with decreased gene expression) | 6 hrs/day, 5 days/week, 15 exposure days <sup>†</sup> | LOAEL                                                      | 1.5                            |

\*In Dorman et al., young male rhesus monkeys were exposed to MnSO<sub>4</sub> through inhalation exposure for 6 hrs/day for 5 days/week. One cohort of monkeys ( $n=4-6$  animals per exposure concentration) was exposed to MnSO<sub>4</sub> in air at 0.06, 0.3, or 1.5 mg Mn/m<sup>3</sup> for 65 exposure days (2005). Another eight monkeys were exposed to MnSO<sub>4</sub> at 1.5 mg Mn/m<sup>3</sup> for 65 days and held for 45 or 90 days before evaluation. A second cohort ( $n=4$  monkeys per time point) was exposed to MnSO<sub>4</sub> at 1.5 mg Mn/m<sup>3</sup> and evaluated after 15 or 33 exposure days. Evaluations included measurement of lung manganese concentrations and evaluation of respiratory histologic changes (Dorman et al., 2005).

<sup>°</sup>Effects were subclinical. Changes were only apparent on post-mortem histopathological exam.

<sup>†</sup>In Erikson et al., young male rhesus monkeys in the control group ( $n=6$ ) were exposed to filtered air for 65 exposure days ( $n=6$ ) (2008). The exposure group monkeys in Erikson et al. were exposed to MnSO<sub>4</sub> through inhalation exposure at 1.5 mg Mn/m<sup>3</sup> for 15 ( $n=4$ ) or 33 ( $n=4$ ) exposure days; or to 1.5 mg Mn/m<sup>3</sup> for 65 exposure days and held for either 45 days ( $n=4$ ) or 90 days ( $n=4$ ) before evaluation (recovery groups). The authors assessed biochemical endpoints indicative of oxidative stress and excitotoxicity in the cerebellum, frontal cortex, caudate, globus pallidus, olfactory cortex, and putamen. Glutamine synthetase (GS), glutamate transporters (GLT-1 and GLAST) and tyrosine hydroxylase (TH) protein levels, metallothionein (MT), GLT-1, GLAST, TH and GS mRNA levels, and total glutathione (GSH) levels were determined for all brain regions (Erikson et al., 2008).

While TCEQ, the petition, and Perry et al. all use the same POD, the TRVs from TCEQ, petition, and Perry et al. use different uncertainty factors to calculate a 24-hour acute manganese TRV (Table 2). Quotes from TCEQ on their UF selections are displayed in Table 3.

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**Table 2.** Information on the uncertainty factors (UFs) and other adjustments used in TCEQ's, the petitioner's, and Perry et al.'s TRV for acute exposure to manganese.

| TRV Source         | TRV ug/m <sup>3</sup> | Uncertainty Factor (UF) Information |                              |                       |                             |                          |          | Human Equivalent Concentration in TRV? | Time Adjustment in TRV? |
|--------------------|-----------------------|-------------------------------------|------------------------------|-----------------------|-----------------------------|--------------------------|----------|----------------------------------------|-------------------------|
|                    |                       | UF <sub>A</sub> Inter-species       | UF <sub>H</sub> Intraspecies | UF <sub>L</sub> LOAEL | UF <sub>S</sub> Sub-chronic | UF <sub>D</sub> Database | Total UF |                                        |                         |
| TCEQ, 2017         | 5.0                   | 3                                   | 10                           | 2                     | NA                          | 6                        | 300*     | No                                     | No <sup>◊</sup>         |
| Petition           | 5.0                   | 10 <sup>†</sup>                     | 10                           | 3                     | NA                          | --                       | 300      | No                                     | No                      |
| Perry et al., 2023 | 5.0                   | 3 <sup>‡</sup>                      | 10                           | 10 <sup>‡</sup>       | NA                          | --                       | 300      | No                                     | No                      |

\*While the total UF is equivalent 360, TCEQ used a total UF of 300 when calculating the TRV. TCEQ has a policy that 300 is the maximum total UF allowed for acute TRVs.

◊TCEQ stated "For the 24-h ReV, the LOAEL/POD of 1.5 mg Mn/m<sup>3</sup> was used as the 24-h PODADJ since the total exposure duration was considerably longer (*i.e.*, 90 h) and lung tissue data from the study indicates that the accumulation of Mn in the lung predominated over the 3-week exposure period. Thus, the PODADJ for derivation of the 24-h ReV is 1.5 mg Mn/m<sup>3</sup>" (2017).

‡The petition states "a lower 3-fold interspecies uncertainty factor could also be supported because a dosimetric adjustment between monkeys and humans is not required as discussed in Dorman et al. (2005). Using a 10-fold factor, the proposed TRV is conservative" (Bridgewater Group, 2022).

‡Perry et al. states that they applied a 3-fold factor for UF<sub>A</sub>, which includes 3-fold for differences in toxicodynamics and a factor of 1 for toxicokinetic differences (2023). The authors also state that the 10-fold UF<sub>L</sub> accounts for both LOAEL-to-NOAEL extrapolation and the lack of data for a continuous 24-h exposure period (Perry et al., 2023).

**Table 3.** TCEQ's statements on the uncertainty factors (UFs) for manganese.

| UFs                             | Page Number of the <a href="#">TCEQ Manganese Document</a> | Direct Quote from TCEQ (2017)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| UF <sub>A</sub><br>Interspecies | 21                                                         | "A UF <sub>A</sub> of <b>3</b> was used to account for potential toxicodynamic differences between rhesus monkeys and humans."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| UF <sub>H</sub><br>Intraspecies | 21                                                         | "A full UF <sub>H</sub> of <b>10</b> was used for intrahuman variability to account for potentially sensitive subpopulations ( <i>e.g.</i> , children, the elderly, those with pre-existing medical conditions)."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| UF <sub>L</sub><br>LOAEL        | 8                                                          | "...Use of a minimal LOAEL-to-NOAEL uncertainty factor is justified as opposed to use of the 5-fold lower no-observed-adverse-effect-level (NOAEL of 0.3 mg Mn/m <sup>3</sup> ) from the subchronic portion of the study due to the very conservative nature of the assessment for derivation of the acute ReVs ( <i>i.e.</i> , actual exposure duration far exceeding those of interest for the 1- and 24-h ReVs, use of a single day of a 3-week exposure for the 1-h ReV duration adjustment, minimal/mild airway inflammatory changes utilized as endpoints in the absence of observed clinical signs)."                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                 | 21                                                         | "A reduced UF <sub>L</sub> of <b>2</b> was used for extrapolation from a LOAEL to a NOAEL since the observed pulmonary pathology was characterized as mild/minor airway inflammatory changes in the absence of observable clinical signs"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| UF <sub>s</sub><br>Subchronic   |                                                            | NA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| UF <sub>D</sub><br>Database     | 21-22                                                      | "A UF <sub>D</sub> of <b>6</b> was used for limitations/uncertainties in the acute/subacute database including the lack of toxicological data on: (1) humans exposed acutely (or subacutely) to either less soluble forms of Mn or the more soluble forms of greater potential concern for the general population; and (2) whether acute/subacute exposure to inhaled Mn has a significant potential for adverse effects on numerous endpoints including developmental neurological effects, and if so (as suggested by the oral developmental database, as well as neurological/neurobehavioral changes being the critical effects based on the intermediate- and chronic duration databases), what exposure concentrations/durations induce them (ATSDR 2012). That is, additional studies involving neurobehavioral effects following gestational and postnatal exposure to airborne Mn are necessary. The addition of developmental neurotoxicology studies using a functional observational battery design and a wide range of well-established measures would result in a more complete inhalation (and oral) database, particularly if non-human primates are used considering that rodents may be a less-than desirable model for neurological effects in humans ( <i>i.e.</i> , rodent models do not appear to be as susceptible to Mn-induced neurotoxicity as humans and monkeys, somewhat diminishing the relevance of chronic Mn inhalation exposure rodent neurological results in regard to their ability to help identify the most sensitive Mn effects that may occur in humans) (see Section 3.12.2 of ATSDR 2012). Additionally, while some acute/subacute studies demonstrate either free-standing NOAELs or LOAELs/LOELs, they do not demonstrate these values in the context of studies adequate to fully characterize dose-response for the endpoints studied. These database limitations result in a low confidence in the acute/subacute database overall (TCEQ 2015), consistent with ATSDR (2012) not deriving an acute duration minimal risk level (MRL) (inhalation or oral)." |

# Proposal for New Acute Manganese TRV

DEQ does not have a final proposal for acute exposure TRV. To aid ATSAC discussion, Table 4 outlines a range of potential proposals for DEQ's acute manganese TRV. Not all potential options are in this table. **DEQ wants to hear from ATSAC members on the benefits and drawbacks of the proposals in Table 4.** DEQ also wants to know if ATSAC members think a better proposal option is available other than those listed in Table 4. ATSAC member feedback will inform DEQ's final proposal.

**Table 4.** Potential options for DEQ's acute manganese TRV for ATSAC to discuss.

| TRV Proposal Name                                                          | TRV (ug/m <sup>3</sup> ) | Uncertainty Factor (UF) Information |                               |                       |                             |                          |           | Human Equivalent Concentration in TRV? | Time Adjustment in TRV? | Notes                                                                                                                              |
|----------------------------------------------------------------------------|--------------------------|-------------------------------------|-------------------------------|-----------------------|-----------------------------|--------------------------|-----------|----------------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------|
|                                                                            |                          | UF <sub>A</sub> Inter-species       | UF <sub>H</sub> Intra-species | UF <sub>L</sub> LOAEL | UF <sub>S</sub> Sub-chronic | UF <sub>D</sub> Database | Total UF* |                                        |                         |                                                                                                                                    |
| <b>Option 1</b><br>TCEQ                                                    | 5.0                      | 3                                   | 10                            | 2                     | NA                          | 6                        | 300       | No                                     | No                      | No changes to TCEQ's 2017 final acute Mn TRV. This includes TCEQ's policy that 300 is the maximum total UF allowed for acute TRVs. |
| <b>Option 2</b><br>TCEQ with no total UF maximum                           | 4.2                      | 3                                   | 10                            | 2                     | NA                          | 6                        | 360       | No                                     | No                      | Removes TCEQ's policy of capping the total UFs to 300 for acute TRVs.                                                              |
| <b>Option 3</b><br>Petition                                                | 5.0                      | 10 <sup>0</sup>                     | 10                            | 3                     | NA                          | --                       | 300       | No                                     | No                      | The proposed TRV is the same as the TCEQ acute value, but some of the UFs are different.                                           |
| <b>Option 4</b><br>Petition with UF <sub>D</sub>                           | 0.8                      | 10                                  | 10                            | 3                     | NA                          | 6                        | 1800      | No                                     | No                      | Compared to the petition, includes an additional UF <sub>D</sub> , which matches the TCEQ UF <sub>D</sub> .                        |
| <b>Option 5</b><br>Petition with UF <sub>D</sub> and lower UF <sub>A</sub> | 2.8                      | 3                                   | 10                            | 3                     | NA                          | 6                        | 540       | No                                     | No                      | Compared to petition, includes the additional database UF <sub>D</sub> , but a lower UF <sub>A</sub> .                             |
| <b>Option 6</b><br>Perry et al. 2023                                       | 5.0                      | 3                                   | 10                            | 10                    | NA                          | --                       | 300       | No                                     | No                      | The proposed TRV is the same as the TCEQ acute value, but some of the UFs are different.                                           |
| <b>Other Suggestions from ATSAC members</b>                                |                          |                                     |                               |                       |                             |                          |           |                                        |                         | <b>Please let DEQ know if you think there is another good option that is not already on this table.</b>                            |

\*Additional options include rounding the total UF to one significant digit (e.g., the total UF for Option 2 would be 400 instead of 360). DEQ has observed that this is regularly done by U.S. EPA and ATSDR.

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## Agency Policy on UFs

Different agencies have different UF recommendations. The TCEQ Guidelines Document includes a table that lists the default UFs recommended by different agencies including the U.S. EPA and ATSDR (TCEQ, 2015). A copy of this table is in Appendix A.

## Policies on Maximum Total UFs

TCEQ has a policy that 300 is the maximum total UF allowed for acute TRVs if three UFs are used and the cumulative UF exceeds 300 (TCEQ, 2015). DEQ is not aware of other authoritative source agencies having a policy like this to cap total UFs for acute TRVs at 300. One TRV option for the manganese acute exposure TRV (option 2 in Table 2) is to remove TCEQ's policy cap of 300 and apply a total UF of 360 instead.

## LOAEL Uncertainty Factor (UF<sub>L</sub>) Considerations

As seen in the Appendix A, UF<sub>L</sub> is an example of how different agencies have different UF approaches. TCEQ uses a UF<sub>L</sub> of 2 to 3 for the LOAEL when the health outcome is mild (TCEQ, 2015); in the case of manganese, TCEQ selected a UF<sub>L</sub> of 2 (Table 3). The CalEPA states that a UF<sub>L</sub> of 6 can be used when mild effects are used to derive an acute Reference Exposure Level (OEHHA, 2008a). The ATSDR uses a UF<sub>L</sub> of 3 when there is a "minimal LOAEL," which is described as minimal effects that represent an early indication of toxicity (Chou et al., 1998).

## Database Uncertainty Factor (UF<sub>D</sub>) Considerations

One key difference between the petition and TCEQ is the absence of a UF<sub>D</sub> database uncertainty factor in the petition. Perry et al. also does not include a UF<sub>D</sub>. Table 3 includes TCEQ's reasoning for including a UF<sub>D</sub> of 6, including the need for additional studies to investigate the potential for developmental neurological effects. TCEQ states "These database limitations result in a low confidence in the acute/subacute database overall (TCEQ, 2015), consistent with ATSDR (2012) not deriving an acute duration minimal risk level (MRL) (inhalation or oral)" (TCEQ, 2017).

DEQ thinks there are several unknowns related to manganese-related neurodevelopmental toxicity that a UF<sub>D</sub> may help protect against. While OEHHA did not develop an acute exposure TRV for manganese due to lack of studies, OEHHA does provide information on why the potential for developmental neurological issues from manganese is a concern (OEHHA, 2008b). OEHHA states that several epidemiology studies have reported correlations between early life exposure to excessive manganese and symptoms of impaired neurodevelopment as revealed on neurobehavioral tests and in poorer academic performance [pg. 451-452; (OEHHA, 2008b)]. For example, in a prospective study of the neurobehavioral effects of *in utero* exposure to manganese, Takser et al. reported an inverse correlation between cord blood manganese at birth and three subscales of psychomotor development (McCarthy scales of children's abilities) measured at three years of age (n= 126): attention (partial r = -0.33, p < 0.01), nonverbal memory (partial r = -0.28, p < 0.01), and hand skills [partial r = -0.22, p < 0.05; (OEHHA, 2008b; Takser et al., 2003)].

OEHHA also highlights eight reasons why children may be more susceptible to manganese toxicity than adults [pg. 461; (OEHHA, 2008b)]. Here are three examples:

- "The newborn's brain is still developing, myelination is incomplete, and the blood-brain barrier is not fully formed (Chan et al., 1992). These conditions facilitate manganese uptake into the central nervous system and increase the risk of attaining toxic levels."
- "The liver of newborns has not yet developed the ability to maintain safe levels of manganese in the bloodstream and brain tissues by excreting excess manganese in the bile, i.e., homeostasis of manganese has not yet developed (Miller et al., 1975)."

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- “Manganese exposures in childhood are associated with impaired neurodevelopment including decrements in intellectual function. Thus, a major toxicodynamic factor that differs between adults and children, namely development of the central nervous system, presents hypersensitive targets for toxicity in the developing infant and child.”

The petitioners state that their proposed TRV (option 3 in Table 4) is protective of respiratory toxicity and that additional uncertainty factors for reproductive and developmental toxicity are unnecessary because of:

1. **Reproductive and Developmental Rat Study:** “The reproductive and developmental toxicity study by McGough and Jardine (2017) involving subchronic exposures in rats at levels much higher than the proposed TRV (up to 8.1 mg/m<sup>3</sup> for up to 714 hours) did not result in reproductive or developmental toxicity, which reduces uncertainty associated with potential reproductive or developmental effects” (Bridgewater Group, 2022).
2. **Neurotoxicity Primate Study:** “Additionally, Dorman et al. (2006b) reported no observable symptoms of neurotoxicity associated with exposures in the 2005 study” (Bridgewater Group, 2022).
3. **PBPK Modeling:** “To further address any uncertainty as to whether neurotoxicity could pose a hazard to humans at the proposed TRV, we used the current human PBPK model to evaluate two exposure scenarios: reoccurring exposures for monthly 24-hour exposures (monthly scenario), and continuous exposure for 3 weeks at the age when manganese levels in brain are predicted to be highest (three week scenario). For both scenarios, the current human PBPK model was used to predict concentrations of manganese in blood, liver, and globus pallidus in males and females. The model predictions indicate that, at all life stages, the levels of manganese in the target tissue of the globus pallidus do not increase significantly over background levels and are lower than tissue NOAELs in the globus pallidus” (Bridgewater Group, 2022).

## 1. Reproductive and Developmental Rat Study

However, McGough and Jardine do not evaluate neurodevelopmental endpoints (2017), the developmental endpoint of concern highlighted by epidemiology studies and OEHHA’s assessment. McGough and Jardine looked for MnCl<sub>2</sub> effects on rat body weight, food consumption, and effects on the entire reproductive system including maternal care. The authors also monitored the survival and growth of the rat’s offspring up to weaning. The authors do measure brain weight, which they conclude “brain weight did not achieve significance and therefore was not positively attributed to treatment” (McGough and Jardine, 2017), but they do not evaluate neurodevelopmental endpoints.

## 2. Neurotoxicity Primate Study

Dorman et al. (2006b) was similar to Dorman et al. (2005) where young male rhesus monkeys were exposed to MnSO<sub>4</sub> through inhalation exposure. Dorman et al. (2006b) reported an association between magnetic resonance imaging (MRI) changes and pallidal manganese concentration in rhesus monkeys following subchronic MnSO<sub>4</sub> inhalation exposure. However, Dorman et al. (2006b) did not evaluate the neonatal human exposure period of greatest concern, and the study was not designed to evaluate neurodevelopmental outcomes, such as very early life exposures leading to persistent cognitive deficits.

## 3. PBPK Modeling

It is DEQ’s understanding that the PBPK model was developed based on the assumption that the globus pallidus is the target tissue for all relevant manganese toxicity in the brain. The petition and Perry et al. state that the globus pallidus is the area of the brain with the highest levels of manganese accumulation following exposure, which is demonstrated in a couple of studies (see Table 6.3.1 in OEHHA, 2008b). However, studies also show that there are other areas of the brain that also accumulate manganese after exposure, though it is at lower levels than the globus pallidus. For example, in Dorman et al. (2006a), even at the lowest dose (60 µg/m<sup>3</sup>) in rhesus monkeys, manganese levels were significantly elevated in four of the eight brain regions examined, globus pallidus, putamen, white matter and cerebellum (OEHHA, 2008b).

Dose response data from studies that petitioners cite correlate globus pallidus manganese concentrations with effects such as hand-eye coordination issues and structural changes to the globus pallidus. DEQ was not able

to find studies that showed correlations between globus pallidus manganese concentrations and the cognitive deficits observed in children that were exposed during the neonatal period. Therefore, while the globus pallidus has been shown to have the highest amount of manganese in the brain following manganese exposure, DEQ does not think there are enough studies currently to know for sure:

- Whether the globus pallidus is the relevant target tissue for neurodevelopmental effects such as impaired cognition following early life exposure
- How much manganese is needed in each brain region to cause neurodevelopmental effects
- What developmental stages are most susceptible to Mn insult
- How long early life exposures need to be to cause neurodevelopmental effects

These are the types of unknowns that a  $UF_D$  protects against. For example, is it possible for manganese inhalation exposure to lead to neurodevelopmental effects from a 24-hour exposure to an area of the brain that is not the globus pallidus at a lower dose than what causes other types of health effects? Is it possible for the mechanism by which manganese may cause developmental neurotoxicity in children is different from the mechanism by which manganese causes the hand-eye coordination and other subtle/transient neurotoxicity in adult workers (as observed in the Roels et al. 1992 study that underlies the chronic noncancer TRV)? DEQ still has these questions.

DEQ's priority is to make sure that the manganese acute TRV is health protective, especially for vulnerable populations such as children during critical developmental windows. DEQ wants to hear from ATSAC members if petitioners provide enough information to ensure that a reduced or absent database uncertainty factor remains health protective for developing children.

## Key Questions for ATSAC

- 1)  $UF_A$ : Do you think the  $UF_A$  should be 3 or 10 or something else? Why?
- 2)  $UF_H$ : Do you think the  $UF_H$  should be 10 or something else? All proposals in Table 4 have a  $UF_H$  of 10.
- 3)  $UF_L$ : Do you think the  $UF_L$  should be 2, 3, 10, or something else? Why?
- 4)  $UF_D$ : Do you agree with the petitioners that there is enough evidence to not have a database uncertainty factor? Why or why not?
  - Do you agree with the TCEQ database UF of 6? Why or why not?
- 5) Total UF: Do you think we should put a cap on the maximum total UF like TCEQ does?
- 6) What proposal option in Table 4 do you like the best and why? If you do not like any of the options listed in this document, why? Would you propose another option for DEQ to consider? Is there other information that DEQ needs to consider in order to choose a proposal option?

## Next Steps

ATSAC member feedback will inform DEQ's proposal for the acute manganese TRV. Kearns & West staff will be in contact soon to set up an ATSAC meeting to listen to ATSAC member's thoughts on the petition and the discussion questions in this framing document. The petitioners will also be invited to attend this ATSAC meeting to give a short overview presentation of the petition. If you have questions or initial feedback, please email Apollonia Goeckner, [apollonia.goeckner@deq.oregon.gov](mailto:apollonia.goeckner@deq.oregon.gov).

## References

ATSDR, 2012. Toxicological Profile for Manganese.

Bridgewater Group, 2022. Supporting Evidence for Petition for Oregon Department of Environmental Quality (ODEQ) Air Toxics Review to Revise the Acute Toxicity Reference Value (TRV) for Acute Manganese Exposure.

- Chan, A.W., Minski, M.J., Lim, L., Lai, J.C., 1992. Changes in brain regional manganese and magnesium levels during postnatal development: modulations by chronic manganese administration. *Metab. Brain Dis.* 7, 21–33.
- Chou, C.-H.S.J., Holler, J., De Rosa, C.T., 1998. Minimal risk levels (MRLs) for hazardous substances. *J Clean Technol Env. Toxicol Occup Med* 7, 1–24.
- Dorman, D.C., Struve, M.F., Gross, E.A., Wong, B.A., Howroyd, P.C., 2005. Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. *Respir. Res.* 6, 1–10.
- Dorman, D.C., Struve, M.F., Marshall, M.W., Parkinson, C.U., James, R.A., Wong, B.A., 2006a. Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. *Toxicol. Sci.* 92, 201–210.
- Dorman, D.C., Struve, M.F., Wong, B.A., Dye, J.A., Robertson, I.D., 2006b. Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. *Toxicol. Sci.* 92, 219–227.
- Erikson, K.M., Dorman, D.C., Lash, L.H., Aschner, M., 2008. Duration of airborne-manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. *Neurotoxicology* 29, 377–385.
- McGough, D., Jardine, L., 2017. A two-generation inhalation reproductive toxicity study upon the exposure to manganese chloride. *Neurotoxicology* 58, 194–202.
- Miller, S.T., Cotzias, G.C., Evert, H.A., 1975. Control of tissue manganese: initial absence and sudden emergence of excretion in the neonatal mouse. *Am. J. Physiol.-Leg. Content* 229, 1080–1084.
- OEHHA, 2008a. Air Toxics Hot Spots Risk Assessment Guidelines: Technical support document for the derivation of noncancer reference exposure levels.
- OEHHA, 2008b. Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries: Manganeses and Compounds Reference Exposure Levels.
- Perry, C.S., Blanchette, A.D., Vivanco, S.N., Verwiel, A.H., Proctor, D.M., 2023. Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese. *Regul. Toxicol. Pharmacol.* 145, 105518.
- Roels, H., Ghyselen, P., Buchet, J.-P., Ceulemans, E., Lauwerys, R., 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Br. J. Ind. Med.* 49, 25.
- Takser, L., Mergler, D., Hellier, G., Sahuquillo, J., Huel, G., 2003. Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology* 24, 667–674.
- TCEQ, 2017. Development Support Document: Manganese and Inorganic Manganese Compounds.
- TCEQ, 2015. TCEQ Guidelines to Develop Toxicity Factors.



## Appendix A

**Table 1.** Copy of Table 3-6 from the [TCEQ Guidelines to Develop Toxicity Factors \(pg. 91\)](#), which is a comparison of UFs used by different organizations (TCEQ, 2015).

| Uncertainty Factors               | TCEQ                                                                                       | USEPA                    | ATSDR                                       | OEHHA                                   | FDA | ECETOC                                                 | Netherlands | Health Canada/ IPCS                         |
|-----------------------------------|--------------------------------------------------------------------------------------------|--------------------------|---------------------------------------------|-----------------------------------------|-----|--------------------------------------------------------|-------------|---------------------------------------------|
| Interspecies, $UF_H$              | $\leq 10$                                                                                  | $\leq 10$                | 1, 3, or 10                                 | $\leq 100$                              | 10  | 2 – 7 (systemic effects)<br>1 (local effects)          | 3           | 10                                          |
| Toxicokinetics, $UF_{H-k}$        | 3                                                                                          | 3                        | --                                          | 1, 3, or 10                             | --  | --                                                     | --          | 2.5                                         |
| Toxicodynamics, $UF_{H-d}$        | 3                                                                                          | 3                        | --                                          | 1, 3, or 10                             | --  | --                                                     | --          | 4                                           |
| Intraspecies, $UF_A$              | $\leq 10$                                                                                  | $\leq 10$                | 1, 3, or 10                                 | $\leq 10$                               | 10  | 5                                                      | 10          | 10                                          |
| Toxicokinetics, $UF_{A-k}$        | 3                                                                                          | 3                        | --                                          | 1, 2, or 3                              | --  | --                                                     | --          | 2.5                                         |
| Toxicodynamics, $UF_{A-d}$        | 3                                                                                          | 3                        | --                                          | 1,2, or 3                               | --  | --                                                     | --          | 4                                           |
| Subchronic to chronic, $UF_{Sub}$ | $\leq 10^*$                                                                                | $\leq 10$                | 1, 3, or 10                                 | 1, 3, or 10                             | 10  | 2 (default)<br>1 (local effects)                       | 1 to 10     | 1 to 100 for $UF_{Sub}$ , $UF_L$ , & $UF_D$ |
| LOAEL to NOAEL, $UF_L$            | 2 – 3* ( $\leq$ mild)<br>6* (mild/severe)<br>10* (severe)                                  | $\leq 10$                | 3 (minimal effects)<br>10 (serious effects) | 6 (mild effects)<br>10 (severe effects) | N/A | 3 (default)<br>$\pm 3$ (depends on severity)           | 1 to 10     | See above                                   |
| Incomplete database, $UF_D$       | $\leq 10^*$ = database deficiency and key study quality, including child/adult differences | $\leq 10$                | N/A                                         | 1 or 3                                  | N/A | 1 (high confidence level)<br>1-2 (medium)<br>< 2 (low) | N/A         | See above                                   |
| Modifying factor, $UF_M$          | N/A                                                                                        | $\leq 10$ (discontinued) | 1 to 10                                     | N/A                                     | N/A | 1 to 10                                                | 1 to 10     | 1 to 10                                     |

\*For TCEQ, since the  $UF_{Sub}$ ,  $UF_L$ , and  $UF_D$  are not based on geometric half values, the actual value for  $UF_{Sub}$ ,  $UF_L$ , and  $UF_D$  will be used to form the final product of all UFs (i.e., use of a 3 will count as a 3 and not as  $10^{0.5}$ ).

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800-452-4011 | TTY: 711 | [deqinfo@deq.oregon.gov](mailto:deqinfo@deq.oregon.gov)

# **Appendix P: ATSAC Meeting #3 Follow Up Information from Petitioner & TCEQ on Manganese**



Innovative solutions  
Sound science

April 8, 2024

Apollonia Goeckner  
Program Coordinator  
Oregon Department of Environmental Quality  
700 NE Multnomah Street, Suite 600  
Portland, OR 97232-4100

**SUBJECT:** Further Clarification Following the ODEQ ATSAC Meeting on April 3, 2024

Dear Ms. Goeckner:

We wanted to thank you for the opportunity to present to the Air Toxics Science Advisory Committee (ATSAC) on April 3, 2024. After our presentation, we continued to listen to the ATSAC's discussion and wish to clarify points relevant to some of the questions asked, based on our work on the toxicology of manganese over the last several years.

Oregon Department of Environmental Quality's (ODEQ's) current 24-hour acute manganese toxicity reference value (TRV) of  $0.3 \mu\text{g}/\text{m}^3$  does not reflect the best available science, and it vastly over-estimates potential risk from 24-hour exposures to manganese in ambient air.

In our opinion, a comprehensive understanding of the current science amply supports an acute TRV of  $5 \mu\text{g}/\text{m}^3$ . The information supporting that value includes the Perry et al. (2023) publication, our presentation at the Society of Environmental Chemistry and Toxicology (SETAC) meeting (Perry et al., 2022), and the recent poster presented at Society of Toxicology (SOT) meeting (Perry et al., 2024).

We appreciate ATSAC's consideration of the proposed acute TRV of  $5 \mu\text{g}/\text{m}^3$ , including whether and how uncertainty factors or exposure adjustment factors apply to that value. Overall, we believe that the physiologically based pharmacokinetic (PBPK) modeling results reduce uncertainty in the derived TRV and, accordingly, reduce the need for conservative uncertainty factors or exposure adjustment factors. Specifically, conservative and appropriate uncertainty factors were already used to develop the proposed acute TRV, and the PBPK modeling results verified that acute exposures at the proposed TRV did not significantly increase tissue manganese levels above background levels maintained by homeostasis. In developing the proposed TRV, we also looked at benchmarks in the literature for air and tissue concentrations and found that an acute TRV of  $5 \mu\text{g}/\text{m}^3$  is protective for respiratory and neurological effects. The best available science supports the proposed TRV value without application of additional uncertainty or exposure adjustment.

In support of ATSAC's further consideration of that position, after reviewing some general information about manganese that is critical to evaluating dose response and developing an acute TRV, below we provide clarifying information about the following two aspects of the ATSAC's discussion regarding the proposed TRV value:

- Whether the point of departure (POD) should be adjusted for duration of exposure, and
- Selection of appropriate uncertainty factors.

### **Manganese is an Essential Nutrient**

As discussed, the TRV for manganese should consider that manganese is an essential nutrient and appropriate uncertainty factors may vary as compared to those used for chemicals and metals which are not essential.

- Manganese demonstrates a U-shaped dose-response curve. We naturally carry a necessary amount of Mn in our bodies from background exposures in diet, water, and ambient air. Too little or too much manganese can create adverse effects.
- For manganese and other essential nutrients, the unnecessary compounding of uncertainty factors applied to study data can result in unnecessarily low toxicity criteria, where exposures are well below background conditions.
- A highly vetted human PBPK model for manganese has been used to verify that the proposed acute TRV is protective.

### **Adjusting the Point of Departure for Study Duration**

As ATSAC discussed, we used the LOAEL of 1.5 mg/m<sup>3</sup> as the point of departure without an adjustment for exposure duration to develop the acute TRV.

Perry et al. (2023) is a peer-reviewed publication. While we received a substantial number of comments from the reviewers, none questioned the approach of not adjusting based on exposure time from the subacute points of departure (PODs). The Perry et al. (2022) presentation and Perry et al. (2024) poster were well-received at scientific meetings. Additionally, the Texas Commission on Environmental Quality (TCEQ)'s 2015 Toxicity Factor Guidance underwent peer review coordinated by Toxicology Excellence for Risk Assessment (TERA). Additionally, the specific approach for 24-hour exposures (TCEQ, 2014) and the Manganese Development Support Document (TCEQ, 2017) underwent public comment. In all cases, the rationale for not time-adjusting the subacute POD was not questioned.

The Dorman et al. (2005) and Erikson et al. (2008) studies in question included exposure periods totaling 90 hours over three weeks and are conservative for developing a 24-hour acute TRV. During their discussion, several ATSAC members considered applying an exposure adjustment factor of 4 to the POD from the Dorman et al. (2005) and Erikson et al. (2008) studies, because exposure in the studies occurred for 6 hours out of 24 hours in

a day rather than continuously for 24 hours. Importantly, the study exposure period was not for a single, 6-hour day, but extended for a total of 90 hours (30 hours per week for a 3-week period).

Moreover, Table 2 of Dorman et al. (2005) presents manganese concentrations in the lung following 1.5 mg/m<sup>3</sup> at 15 days (90 hours), 33 days (198 hours) and 65 days (390 hours) of total exposure. Mn concentrations were essentially equal at each time point, ranging from 0.33 to 0.39 µg/g tissue, demonstrating that manganese tissue concentrations in the target tissue of the lung had reached steady state by the 90 hour time point. As such, we would not expect lung tissue levels to be higher following a single 24 hour exposure than that for 6 hours per day, for 15 days (or a total of 90 exposure hours), which is the exposure at the POD.

USEPA (1994) recognized the uncertainty in assuming a temporal relationship of toxicity and duration adjustment. According to EPA: “The rationale for this linear prorate adjustment is that the resultant human exposure concentration should be the concentration (C) x time (T) equivalent of the experimental animal exposure level. This adjustment is weakly founded because steady-state conditions may not be reached in laboratory animals for some chemicals and intermittent regimens (applicable to extrapolation from shorter to longer-term exposures).” EPA’s analysis applies to manganese and the POD because as described above, lung tissue had reached steady state within the exposure period used to define the POD. In short, given that manganese for 6 hours per day, for 15 days, had reached steady state concentrations in the lung, it is not reasonable to include additional time adjustment to account for 6 hours per day of exposure as compared to 24 hours/day.

USEPA has also affirmed the use of PBPK modeling as the first and best means of extrapolating one dose-duration scenario to another. In its “Review of the Reference Dose and Reference Concentration Guidance Process” (2002), USEPA recommends that “the optimal approach for extrapolating from one dose-duration response situation to another is the use of a physiologically based pharmacokinetic model (PBPK) model.” Our PBPK model considered two scenarios: monthly 24-hour exposures for a lifetime and a 3-week continuous exposure period consistent with the TRV and the Short-term Guideline Concentration. In neither case were manganese concentrations in the brain, liver, and blood significantly greater than background levels. The results of the PBPK model for manganese support that no additional exposure adjustment factor is necessary to protect acute exposures.

The decision to use the lowest-observed-adverse-effect level (LOAEL) without adjustment in Perry et al. (2023) also considered TCEQ’s rationale derived from its “Guidelines to Develop Toxicity Factors” (2015). TCEQ identifies that subacute toxicity studies (i.e., repeated or continuous exposure to a chemical greater than one day to one month or less) may be of greatest value for developing 24-hour acute guideline values. The Dorman et al. (2005) and Erikson et al. (2008) studies are both subacute toxicity studies. TCEQ guidance recommends that “if it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute study can be used as the 24-hour

POD without adjustment.” This is the approach adopted by TCEQ for manganese. The unique properties of manganese were recognized by TCEQ when it used the subacute LOAEL without adjustment because:

“accumulation of manganese in the lung predominated over the 3-week exposure period. That is, after 15 exposure days, lung Mn was statistically significantly increased over controls, demonstrating that toxicokinetic clearance did not occur after each daily 6-h exposure but rather that Mn accumulation in the lung occurred from day to day, and in fact appears to have reached steady state (see Table 2 of Dorman et al. 2005).”

## Uncertainty Factors

As discussed during the ATSAC meeting on April 3, 2024, there are three areas where a range of uncertainty factors (UFs) was considered in ODEQ’s Framework Document (ODEQ, 2024). Consensus appeared to be reached for the other two UFs: intraspecies UF ( $UF_H = 10$ ) and subchronic UF ( $UF_S = 1$ ). The three factors are discussed below:

- Interspecies uncertainty ( $UF_A$ ) – Options of 3 and 10 were considered although a factor of 3 was recommended in Perry et al. (2023), based on the primate study from which the LOAEL was derived. PBPK modeling supports very similar Mn toxicokinetics between monkeys and humans.
- LOAEL to NOAEL ( $UF_L$ ) – Using a factor of 3 would have been appropriate for the mild effects observed in the study, but Perry et al. (2023) used 10 to also address some additional uncertainty with the study duration of 6 hours per day for 5 days per week for 3 weeks (90 hours), rather than 24 consecutive hours of exposure. As stated in Perry et al. (2023), the proposed acute TRV included “a 10-fold uncertainty factor to account for LOAEL-to-NOAEL extrapolation and the lack of data for a continuous 24-h exposure period (emphasis added).”
- Database ( $UF_D$ ) – Options from 1 to 6 were considered. However, based on the results of the PBPK modeling, which captured early, sensitive lifestages (starting at birth), and benchmarks for exposure and tissue concentrations in the literature, a further database uncertainty factor is not necessary.

In combination, the overall UF recommended in Perry et al. (2023) was 300. However, if a less conservative  $UF_L$  of 3 is used, and a 4-fold time adjustment is applied, the resulting TRV would be essentially equivalent. The combined time adjustment and uncertainty factor would be 400, as compared to 300. However, we believe that no time adjustment is needed given that the POD was measured under steady state conditions in the lung.

## Additional Lines of Evidence Supporting a $5 \mu\text{g}/\text{m}^3$ Acute TRV

In Perry et al. (2023) and the SOT poster (Perry et al., 2024), additional lines of evidence were provided supporting the acute TRV of  $5 \mu\text{g}/\text{m}^3$ .

- In a rat developmental drinking water study with Mn up to 4 mg/L, Oshiro et al. (2022) reported no cognitive impairment among offspring when combined with maternal stress.
- Epidemiologic studies in children have shown cognitive effects in children associated with elevated blood manganese, but the range of blood Mn levels associated with cognitive effects varies considerably (Bhang et al., 2013; Haynes et al., 2015). Blood Mn levels in the PBPK model were consistent with background.

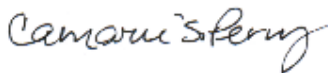
The proposed acute guideline of 5  $\mu\text{g}/\text{m}^3$  is conservative relative to chronic inhalation values.

- Bailey et al. (2009) proposed 2  $\mu\text{g}/\text{m}^3$  to 7  $\mu\text{g}/\text{m}^3$  as chronic reference concentrations.
- Schroeter et al. (2011) and Gentry et al. (2017) predicted that homeostasis maintains Mn levels in the brain target tissue at airborne concentrations below 10  $\mu\text{g}/\text{m}^3$ .
- Yoon et al. (2011) indicated that maternal and fetal blood and brain Mn levels were still within the normal range at airborne concentrations less than 10  $\mu\text{g}/\text{m}^3$ .

## Summary

Manganese is a well-studied essential nutrient with advanced PBPK modeling to support developing an acute TRV. It is paramount, in revising DEQ's existing acute TRV, to consider the weight of the evidence (including the significant new information from the PBPK model) rather than simply compiling default adjustment and uncertainty factors. The PBPK model is the tool EPA has identified for this purpose. In this instance, the PBPK model provides support that regardless of exposure duration adjustment and UFs, an acute TRV of 5  $\mu\text{g}/\text{m}^3$  is protective of public health as presented in our peer-reviewed paper, SOT poster, and SETAC presentation, and as recommended by TCEQ. If uncertainty factors become so high that the resulting value is similar to the ATSDR chronic Minimal Risk Level (MRL) (0.3  $\mu\text{g}/\text{m}^3$ ), then ODEQ should withdraw the current acute TRV and wait for additional information before deriving an acute TRV.

Sincerely,



Camarie Perry  
Senior Scientist II



Ann Holbrow Verwiel  
Senior Managing Scientist

Attachment A - Response to Specific Comments at the ATSAC Meeting on April 3,  
2024

Attachment B - References

**ATTACHMENT A**

**Responses to Specific  
Comments at the ATSAC  
Meeting on April 3, 2024**



## **Attachment A: Responses to Specific Comments at the ATSAC Meeting on April 3, 2024**

We are providing responses to the following questions raised during the ATSAC's April 3, 2024 meeting discussion of ODEQ's 24-hour toxicity reference value (TRV) for manganese (Mn) in case they are useful for further deliberations.

### **1. How were in utero exposures addressed in deriving the proposed 24-hour TRV?**

In utero exposure was addressed by multiple lines of evidence. While the PBPK modeling started at birth (0 years of age), there are pregnancy modeling results in the literature. Yoon et al., 2011 performed PBPK modeling for fetal and neonatal Mn exposures in humans. Their modeled results showed similar or lower internal Mn levels in the brains of fetuses/neonates relative to the adult/pregnant female at Mn air concentrations as high as  $10 \mu\text{g}/\text{m}^3$ . Further, the Mn levels predicted in the fetus/neonate were within the normal range. In Perry et al., 2023 blood manganese concentrations in adult females were essentially consistent with background exposures at  $5 \mu\text{g}/\text{m}^3$ , further supporting that in utero Mn exposures at the proposed TRV will be consistent with background. These results indicate acute exposures at  $5 \mu\text{g}/\text{m}^3$ , would not result in increased Mn exposure to the fetus and thus not adversely impact fetal development.

### **2. Why were the exposure scenarios chosen (24-hours once per month and continuously for 3 weeks)?**

Acute exposure scenarios were chosen to address potential operational conditions of emission sources. The continuous 24-hour exposure once per month scenario represents an occasional but repeated excursion to the TRV level, which would result in twelve 24-hour exposures per year. As described in Perry et al. 2023, the 3-week scenario was also assessed because the TRV is derived from the short-term guideline concentration (SGC), which is designed to be protective of exposures for 'a few weeks.' The most relevant exposure scenario for the 24-hour TRV is the 24-hour exposure which was conservatively assumed to occur monthly.

### **3. At proposed acute TRV, what percent of total Mn dose is from inhalation vs. background?**

The results of the PBPK model predict tissue concentrations in the globus pallidus would be 3 percent higher than in concentrations at background exposure levels for a 3 to 10-year old exposed to manganese in air at  $5 \mu\text{g}/\text{m}^3$ . Increases for other age groups were lower. These tissue concentrations account for homeostatic mechanisms regulating the concentrations of manganese in blood.

#### **4. Are the key studies are based on a single dose?**

The key studies supporting the proposed 24-hour TRV are based on a single exposure concentration of 1.5 mg/m<sup>3</sup>, occurring for 6 hours per day, 5 days per week, for 15 days, for a total 90-hour exposure period. However, as discussed in Perry et al., 2023 and our April 8, 2024 letter, the same studies included multiple doses evaluated for longer-term exposures (65 days). This exposure period is not consistent with an acute TRV scenario. Our literature search did not identify any studies evaluating a single 24-hour exposure, and we believe the Point of Departure (POD) is conservative as the basis of an acute TRV.

#### **5. Were control animals used in key studies?**

Control animals were used in the Dorman et al., 2005 and Erikson et al., 2008 studies. The animals were exposed to the same filtered air as the test monkeys for 65 days (corresponding to the longer term exposures in the studies) and did not have observed effects. The control animal results from Dorman et al., 2005 were presented in Table 3 of Perry et al., 2023, and the Erikson et al., 2008 control results are presented in the referenced paper.

#### **6. Why are there short-term increases in tissue concentrations in graphical displays for the modeling results before exposure occurred?**

The modeling involves a combination of models, developed for different age groups, and each model had parameters averaged over periods of time, which caused some peaks unrelated to exposure. From Perry et al., 2023 Figure 1, an excerpt of which was shown in the slides, the 3-week exposure graph has a small (<0.01 µg/g) increase in Mn concentrations in the globus pallidus followed by a larger increase related to exposure followed by a decrease over time. The two increases occur between 3.25 and 3.5 years of age. The first, small peak, which is also apparent for the background exposure scenario, is due to the tissue volume changing, as this is the near beginning of the child model, and it takes a bit of time to even out. The second peak is from the start of the 3-week exposure to 5 µg/m<sup>3</sup> Mn.

#### **7. Were background exposures in key studies of primates comparable to background exposures in PBPK model?**

Table 1 in Erikson, et al., 2008, presents several average tissue concentrations for the primates in the control group that can be compared to estimated tissue concentrations from the PBPK model for background exposures for 3 to 10 year old children, which are presented in Figure 3 of Perry et al., 2024. Table 1 below presents these results for tissues common to both sets of results, and shows that the results are comparable.

**Table 1. Comparison of Erikson et al., 2008 tissue concentrations in control animals to predicted background tissue concentrations in humans from the PBPK modeling (µg/g)**

| <b>Tissue</b>          | <b>Control Group (Erikson et al., 2008)</b> | <b>Background from PBPK modeling (males 3 to 10 years old) (Perry et al., 2024)</b> |
|------------------------|---------------------------------------------|-------------------------------------------------------------------------------------|
| <b>Globus pallidus</b> | 0.48                                        | 0.54                                                                                |
| <b>Cerebellum</b>      | 0.44                                        | 0.38                                                                                |
| <b>Blood</b>           | 0.01                                        | 0.011                                                                               |

## **ATTACHMENT B**

# **References**

## References

- Bailey LA, Goodman JE, Beck BD. 2009. Proposal for a revised Reference Concentration (RfC) for manganese based on recent epidemiological studies. *Regul Toxicol Pharmacol* 55:3.
- Bhang S-Y, Cho S-C, Kim J-W, Hong Y-C, et al. 2013. Relationship between blood manganese levels and children's attention, cognition, behavior, and academic performance—A nationwide cross-sectional study. *Environ Res* 126:9-16.
- Dorman DC, Struve MF, Gross EA, Wong BA, et al. 2005. Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. *Respir Res* 6:121.
- Erikson KM, Dorman DC, Lash LH, Aschner M. 2008. Duration of airborne manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. *Neurotoxicology* 29:3.
- Gentry, PR, Van Landingham C, Fuller WG, Sulsky, SI et al. 2017. A tissue dose-based comparative exposure assessment of manganese using physiologically based pharmacokinetic modeling—the importance of homeostatic control for an essential metal. *Toxicol Appl Pharmacol*. 322:27–40.
- Haynes EN, Sucharew H, Kuhnel P, Alden J, et al. 2015. Manganese exposure and neurocognitive outcomes in rural school-age children: The Communities Actively Researching Exposure Study (Ohio, USA). *Environ Health Perspect* 123:10.
- O’Neal SL, Zheng W. 2015. Manganese toxicity upon overexposure: a decade in review. *Curr Environ Health Rep* 2 (3), 315–328. <https://doi.org/10.1007/s40572-015-0056-x>. Sep.
- Oregon Department of Environmental Quality (DEQ). 2024. Framing Document for DEQ’s Air Toxics Science Advisory Committee, Petition for Changes to DEQ’s Manganese Toxicity Reference Value for Acute Exposure.
- Oshiro WM, McDaniel KM, Beasley TE, Moser V, et al. 2022. Impacts of a perinatal exposure to manganese coupled with maternal stress in rats: Learning, memory and attentional function in exposed offspring. *Neurotoxicol Teratol* 91: 107077.
- Perry C, Verwiel A, Antonijevic T, Vivanco S, Proctor D. 2022. Short-term environmental inhalation toxicity criteria for airborne manganese protective of neurological and respiratory effects for use in air toxics risk assessment. Presented at the Society of Environmental Toxicology and Chemistry North America’s 43rd Annual Meeting, Pittsburgh, PA, November 13–17, 2022.

Perry C, Vivanco S, Verwiel A, Proctor D. 2024. Derivation of Manganese 24-hour Acute Inhalation Guideline Protective of Respiratory and Neurological Effects. Abstract 4751, Society of Toxicology Annual Meeting, Salt Lake City, UT, March.

Perry CS, Blanchette AD, Vivanco SN, Verwiel AH, Proctor DM. 2023. Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese. *Regul Toxicol Pharmacol* 145:105518.

Schroeter JD, Nong A, Yoon M, Taylor MD et al. 2011. Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multi-route physiologically based pharmacokinetic models. *Toxicol Sci* 120:2

Texas Council on Environmental Quality (TCEQ). 2014. TCEQ Guidelines to Develop 24-hour Inhalation Reference Values. June 16.

Texas Council on Environmental Quality (TCEQ). 2015. Guidelines to Develop Toxicity Factors. RG-442.

Texas Council on Environmental Quality (TCEQ). 2017. Manganese and inorganic manganese compounds, CAS Registry Number: 7439-96-5 (except inorganic manganese compounds in the (VII) oxidation state such as permanganates). Development support document.

U. S. Environmental Protection Agency (USEPA). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. October

U. S. Environmental Protection Agency (USEPA). 2002. A Review of the Reference Dose and reference Concentration Processes. EPA/630/P-02/002F. December.

Yoon M, Schroeter JD, Nong A, Taylor MD et al. 2011. Physiologically based pharmacokinetic modeling of fetal and neonatal manganese exposure in humans: describing manganese homeostasis during development. *Toxicol Sci* 122:297–316.

## Holly Dixon

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**From:** Travis Quarles <tquarles@bridgeh2o.com>  
**Sent:** Tuesday, May 7, 2024 5:08 PM  
**To:** GOECKNER Apollonia \* DEQ  
**Cc:** GSKA JR \* DEQ; Holly Dixon  
**Subject:** Re: ATSAC Meeting 3: Follow Up Manganese Questions  
**Attachments:** Letter\_additional PBPK modeling\_2024-05-07.pdf

**Follow Up Flag:** Follow up  
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Hi Apple,

Thanks for your April 15 email concerning the work DEQ, OHA and ATSAC are doing to review the acute manganese TRV value. We are grateful for your consideration of the report that ToxStrategies prepared as well as the peer-reviewed research discussed. The ToxStrategies report was submitted to you on April 8, 2024, following ATSAC's meeting earlier in the month, and sought to address issues that arose at the meeting. Today, we submit a single additional data point that assists in confirming ToxStrategies' prior research, and we hope that there is still time for your team to take it into consideration.

Since our last correspondence, ToxStrategies completed supplemental PBPK modeling that will be submitted for publication in *Regulatory Toxicology and Pharmacology*. That work was to further assess whether it is necessary to adjust the point of departure (POD) under consideration to account for the 6-hour per day exposure duration in the underlying animal studies.

ToxStrategies' most recent modeling has determined that there is essentially no difference between the PBPK-model predicted maximum manganese tissue concentrations for the exposure scenarios in the underlying studies (6-hours per day, 5-days per week, 3 weeks), as compared to a 24-hour (acute) exposure scenario.

ToxStrategies' latest work is presented in the attached letter report. The data confirms the prior conclusions that: (1) no time-adjustment to the POD is needed to derive a health-protective acute (24-hour) manganese TRV; and (2) the proposed TRV of 5 µg/m<sup>3</sup> is protective.

We understand that, at this time, DEQ is not seeking further information on the petition to change the acute manganese TRV. However, ToxStrategies' latest PBPK modeling data is available now and it reflects the latest science on this issue. Therefore, we submit it in time for it to be considered while agency and ATSAC review of the acute manganese TRV is underway, and before any future TRV rulemaking based on that review is initiated. We would appreciate your consideration of this one additional point of reference.

Please let me know if you have any follow-up questions.

Thank you,  
Travis

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Travis Quarles | **BRIDGEWATER GROUP**

7100 SW Hampton St.; Suite 235 | Tigard, OR 97223  
c. 503.327.9679 | o. 503.212.2516  
tquarles@bridgeh2o.com | www.bridgeh2o.com

On Apr 15, 2024, at 3:54 PM, GOECKNER Apollonia \* DEQ <Apollonia.GOECKNER@deq.oregon.gov> wrote:

Travis,

We wanted to provide you, and ToxStrategies, with the materials and email communication that we sent to ATSAC members as a follow-up from the materials you all provided based on the discussion at the ATSAC meeting regarding the Mn petition. Materials linked below (the document from ToxStrategies and the email from TCEQ) have also been posted to the ATSAC meeting page. We will provide any future responses from the ATSAC members to these materials on the ATSAC meeting page as well.

We will no longer be accepting further information on this petition from your team – please use the next opportunity for formal feedback that will occur during the TRV Rulemaking process to provide any additional resources, comments, or feedback.

Thank you all again for the excellent discussion.

Best,  
Apple



**Apollonia (Apple) Goeckner | Program Coordinator**

Oregon Department of Environmental Quality  
700 NE Multnomah St., Suite 600  
Portland, Oregon 97232 - 4100  
P: 503.869.0026  
Pronouns: She/Her/Hers

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**From:** GOECKNER Apollonia \* DEQ

**Sent:** Friday, April 12, 2024 11:10 AM

**To:** John Budroe <[jdbudroe@gmail.com](mailto:jdbudroe@gmail.com)>; Dong, Qiaoxiang@CDPR <[Qiaoxiang.Dong@cdpr.ca.gov](mailto:Qiaoxiang.Dong@cdpr.ca.gov)>; Jeff Fowles <[jfowles101@gmail.com](mailto:jfowles101@gmail.com)>; Tilton, Susan C <[susan.tilton@oregonstate.edu](mailto:susan.tilton@oregonstate.edu)>; Stanek, John



<[Stanek.John@epa.gov](mailto:Stanek.John@epa.gov)>; John Vandenberg, Ph.D. <[john.vandenberg@duke.edu](mailto:john.vandenberg@duke.edu)>

Cc: Holly Dixon <[Holly.M.Dixon@oha.oregon.gov](mailto:Holly.M.Dixon@oha.oregon.gov)>; Farrer David G <[DAVID.G.FARRER@oha.oregon.gov](mailto:DAVID.G.FARRER@oha.oregon.gov)>;

MACMILLAN Susan \* DEQ <[Susan.MACMILLAN@deq.oregon.gov](mailto:Susan.MACMILLAN@deq.oregon.gov)>; GISKA JR \* DEQ

<[JR.GISKA@deq.oregon.gov](mailto:JR.GISKA@deq.oregon.gov)>

**Subject:** ATSAC Meeting 3: Follow Up Manganese Questions

Hi ATSAC Members,

Thank you all again for your participation and thoughtful feedback during the ATSAC meeting last week.

**New Update:** This week we received a [document from ToxStrategies](#) that includes further clarifications and follow-up after the ATSAC meeting. We also received an [email](#) from the author of the Texas Commission on Environmental Quality (TCEQ) Manganese Development Support Document, Joseph Haney, about the exposure duration adjustment. We wanted to immediately share these documents with you.

**Request:** Based on these additional materials, we compiled three additional questions for you all to answer. Please read the ToxStrategies response document and TCEQ email to provide full context for the questions.

**Please reply-all to this email with your answers to these questions before 4/26.**

1. Does Dorman et al. 2005 (see Table 2 specifically) support ToxStrategies' statement on page 3 of their response document?

*"As such, we would not expect lung tissue levels to be higher following a single 24 hour exposure than that for 6 hours per day, for 15 days (or a total of 90 exposure hours), which is the exposure at the POD." – ToxStrategies Response pg. 3*

If you have questions about Dorman et al. 2005 methods, we attached the paper directly to this email. Figure 1 in Dorman et al. is an overview of the experimental design. Exposure and necropsy procedures are detailed on page 3; for example, Dorman et al. states that "necropsies were performed the day following the last inhalation exposure (i.e., 12-18 hr after termination of the final inhalation exposure)."

2. ToxStrategies highlights TCEQ's guidance related to time adjustments:

*"TCEQ guidance recommends that 'if it is reasonable to assume that steady state has been achieved, or toxicodynamics indicate that no additional toxic effect would be expected to occur with the subacute exposure duration, the POD from the subacute study can be used as the 24-hour POD without adjustment.'" – ToxStrategies Response pg. 3*

Do you agree that the conditions mentioned in this quote from TCEQ guidance are met in the Dorman et al. 2005 and Erikson et al. 2008 study? Do you agree with the TCEQ guidance?

3. Given the additional information from ToxStrategies and TCEQ, what is your current recommendation about an exposure time adjustment and/or uncertainty factors and why?

Attached is a compilation of the three worksheets we received after the 4/3 meeting (see page 2). Please edit the worksheet attachment, if applicable, and email it back to us.

Kearns & West and DEQ are still working on meeting minutes for the 4/3 ATSAC meeting. We will send those to you all to review once they are ready.

Thank you,  
ATSAC Governance Team

**Apollonia (Apple) Goeckner | Program Coordinator**

Oregon Department of Environmental Quality

700 NE Multnomah St., Suite 600

Portland, Oregon 97232 - 4100

P: 503.869.0026

Pronouns: She/Her/Hers



Innovative solutions  
Sound science

May 7, 2024

Mr. Travis Quarles  
Bridgewater Group  
7100 SW Hampton Street, Suite 235  
Tigard, OR 97223

**SUBJECT:** PBPK Modeling Analysis Supports that a Time Adjustment Factor is Not Necessary for the Proposed Manganese Acute TRV

Dear Travis:

As you know, ToxStrategies developed and published an acute guideline for manganese (Mn) of  $5 \mu\text{g}/\text{m}^3$  (Perry et al, 2023)<sup>1</sup>, which has been recommended to Oregon Department of Environmental Quality (ODEQ) as a scientific basis for the Agency's 24-hour acute toxicity reference value (TRV). During the Air Toxics Science Advisory Committee's (ATSAC's) April 3, 2024 panel discussion of the Mn Acute (24-hour exposure) TRV, several members questioned whether the point of departure (POD) under consideration should be adjusted for the 6 hour per day duration of exposure in the animal study, and discussed reducing the POD by a factor of four. We previously provided information to you supporting the use of the POD without time adjustment.

This letter presents for consideration the results of our recent additional work to further evaluate the POD using physiologically-based pharmacokinetic (PBPK) modeling. Specifically, we conducted PBPK modeling to replicate the exposure timeframe in the two monkey studies from which the POD was derived (Dorman et al. 2005 and Erikson et al. 2008).<sup>2</sup> We modeled the Mn tissue dose associated with exposure consistent with the monkey studies of 6 hours/day, 5 days/week, for 3 weeks (90-hour scenario) and compared the results to that for a single 24-hour exposure (24-hour scenario) at the proposed acute Mn TRV ( $5 \mu\text{g}/\text{m}^3$ ). Because our previously published modeling results indicated that the highest tissue Mn occurred at approximately 3.375 years of age in males, the 3-10 year age

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<sup>1</sup> Perry CS, Blanchette AD, Vivanco SN, Verwiel AH, Proctor DM. 2023. Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese. Regul Toxicol Pharmacol 145:105518.

<sup>2</sup> Dorman, DC, Struve MF, Gross EA, Wong BA et al. 2005. Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. Respir Res. 6:121. And Erikson, L.M., Dorman, D.C., Lash, L.H., Aschner, M., 2008. Duration of airborne manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. Neurotoxicology 29:3.

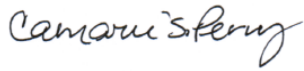
group was the focus of the additional modeling, and because the POD is for respiratory and neurological effects, we evaluated (and present below) results for the lung as well as all brain regions.

As shown in Figure 1 and Table 1, there is essentially no difference between the model-predicted maximum Mn tissue concentrations for the 90-hour exposure and the 24-hour scenarios in the target tissues of the brain and lung. Mn concentrations in the globus pallidus and lung are predicted to increase slightly above background in both exposure scenarios. But, there is no meaningful difference in Mn concentrations in brain or lung tissues between each scenario or with background ( $<0.01 \mu\text{g/g}$ ; Table 1). This information provides further support for the conclusion that no time-adjustment to the POD is needed for deriving a health protective 24-hour TRV.

In summary, ToxStrategies' expanded PBPK modeling analysis further supports the conclusion that the proposed TRV of  $5 \mu\text{g}/\text{m}^3$  is protective for 24-hour exposures to manganese, and that a duration adjustment to the POD is not necessary. In addition, we will be submitting this analysis as a brief communication for publication in *Regulatory Toxicology and Pharmacology*.

Please let us know if you have any questions regarding our additional modeling and results.

Sincerely,



Camarie S. Perry  
Senior Scientist II

Table and Figure

**Table 1. Results of PBPK modeling for manganese ( $\mu\text{g/g}$ ) based on background Mn in ambient air ( $0.015 \mu\text{g/m}^3$ ), diet, and additional inhalation exposure at the proposed TRV of  $5 \mu\text{g/m}^3$  for 24- and 90-hour exposures**

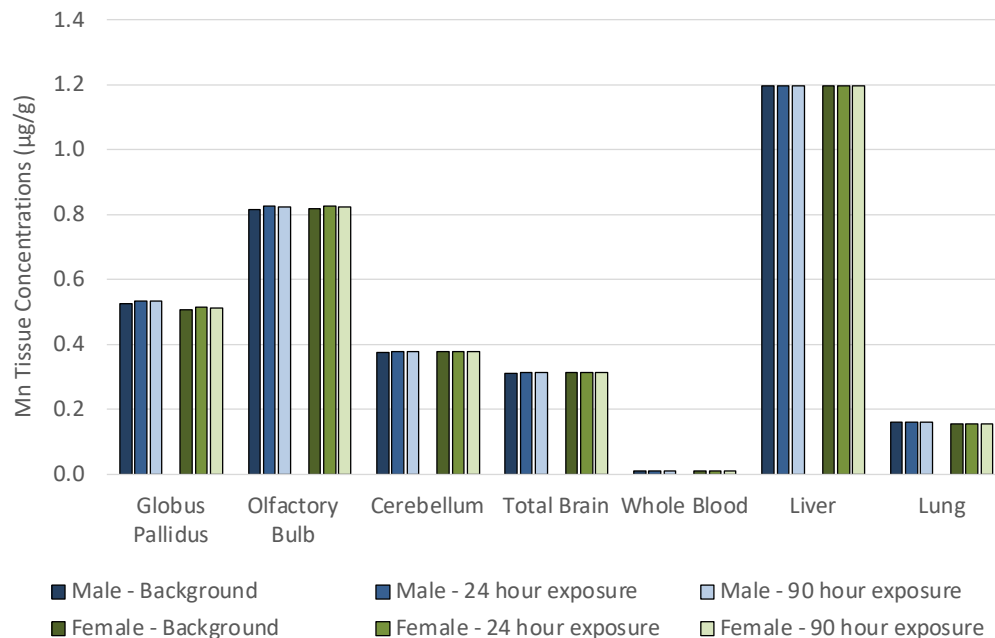
| Modeled Compartment | Male               |                      | Female             |                      |
|---------------------|--------------------|----------------------|--------------------|----------------------|
|                     | 24 hr <sup>1</sup> | 90 hr <sup>1,2</sup> | 24 hr <sup>1</sup> | 90 hr <sup>1,2</sup> |
| Globus Pallidus     | 0.535              | 0.532                | 0.514              | 0.511                |
| Olfactory Bulb      | 0.826              | 0.823                | 0.828              | 0.825                |
| Cerebellum          | 0.377              | 0.377                | 0.379              | 0.378                |
| Total Brain         | 0.313              | 0.313                | 0.314              | 0.314                |
| Lung                | 0.162              | 0.162                | 0.156              | 0.156                |
| Whole Blood         | 0.0116             | 0.0114               | 0.0117             | 0.0115               |
| Liver               | 1.20               | 1.20                 | 1.20               | 1.20                 |
| Nose <sup>3</sup>   | 4.60               | 13.3                 | 4.60               | 13.3                 |
| Bone                | 0.0724             | 0.0724               | 0.0734             | 0.0734               |

<sup>1</sup> To be consistent, the 24-hour and 90-hour exposures reported in Table 1 were evaluated starting at 3.375 years, which is when the elevated background from the earlier time period for 3-year olds becomes more consistent (Figure 2). The 24-hr exposure values in Table 1 differ slightly from the values in Perry et al. (2023) because the monthly 24-hr exposures in Perry et al. started at three years during which time background exposures were higher.

<sup>2</sup> 6 hours/day, 5 days/week for 3 weeks

<sup>3</sup> The model predicted that that maximum Mn levels in the nose are higher than background, and higher in the 90-hour scenario compared to the 24-hour scenario because tissue half-life in the nose is longer (5 days) than in other tissues. Importantly, increased Mn in nasal tissue did not result in any significant change to levels in lung or brain tissues for either scenario compared to background.

**Figure 1: Predicted Mn Tissue Concentrations in 3 to 10 year olds ( $\mu\text{g/g}$ )**



## Farrer David G

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**From:** Holly Dixon  
**Sent:** Friday, April 12, 2024 10:34 AM  
**To:** Joseph Haney  
**Subject:** RE: Exposure Duration Adjustments

Kip,

Thank you for reaching out and sending me this information on the exposure duration adjustment. We are going to reach out to our Oregon Air Toxics Science Advisory Committee today to provide them with the information you included in your email as well as additional information we received from ToxStrategies.

Thanks again,

Holly

Holly Dixon, PhD (she/her)  
Public Health Toxicologist  
Oregon Health Authority | Public Health Division  
holly.m.dixon@oha.oregon.gov | 971-388-9819

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**From:** Joseph Haney <Joseph.Haney@tceq.texas.gov>  
**Sent:** Tuesday, April 9, 2024 6:53 AM  
**To:** Holly Dixon <Holly.M.Dixon@oha.oregon.gov>  
**Subject:** Exposure Duration Adjustments

You don't often get email from [joseph.haney@tceq.texas.gov](mailto:joseph.haney@tceq.texas.gov). [Learn why this is important](#)

**Think twice** before clicking on links or opening attachments. This email came from outside our organization and might not be safe. If you are not expecting an attachment, contact the sender before opening it.

Dr. Dixon:

Camarie Perry with ToxStrategies called me the other day to briefly talk about exposure duration adjustments. Below is a quick summary of some of my perspectives on the subject that I conveyed to her, which she said you may have some interest in as well. Maybe it could further conversations between y'all, and I'm also available for general conversation on the subject.

Reasoned scientific judgment is critical when justifying duration adjustments in deriving toxicity factors, and consideration of TK/TD half-life relative to the duration between exposures is important. For example, if a chemical directly causes CNS effects and even though workers are exposed 8 h/day each day of the work week, both the chemical and all effects entirely clear overnight, each daily exposure is essentially operating as an independent acute exposure experiment as there is no accumulation of dose or effect. By contrast, if a chemical or its toxic metabolite accumulates in a target organ with each daily exposure or causes some effect that does not entirely reverse overnight but rather accumulates with each daily exposure to ultimately produce an observable adverse effect, each daily exposure is not operating as an independent acute experiment and effects would be expected to increase day to day with increased exposure duration. For such chemicals, if the total exposure duration appreciably exceeds that of interest for derivation of a toxicity factor (e.g., 90 hours vs. 24 hours), then it may not be necessary to use an 8- or 6-hour/24-hour duration

adjustment to derive a 24-hour value since it was not the single day exposure that produced the effect, it was the accumulation of dose and/or effect that ultimately produce the adverse effect observed at the end of the exposure regimen.

This latter scenario is one that applies to the 24-h Mn ReV Camarie referred to in our discussion. For example, that DSD states [*emphasis added*], “This minimal LOAEL will be applied to exposure durations up to 24 h of exposure since study data demonstrated that the *accumulation of Mn in the lung predominated over the 90-h total, 3-week exposure period*. That is, *after 15 exposure days, lung Mn was statistically significantly increased over controls*, demonstrating that *toxicokinetic clearance did not occur after each daily 6-h exposure* but rather that *Mn accumulation in the lung occurred from day to day*, and in fact appears to have reached steady state (see Table 2 of Dorman et al. 2005), supporting use of results from this 90-h total exposure for derivation of a 24-h value.”... “For the 24-h ReV, the LOAEL/POD of 1.5 mg Mn/m<sup>3</sup> was used as the 24-h POD<sub>ADJ</sub> since the total exposure duration was considerably longer (i.e., 90 h) and *lung tissue data from the study indicates that the accumulation of Mn in the lung predominated over the 3-week exposure period*. Thus, the POD<sub>ADJ</sub> for derivation of the 24-h ReV is 1.5 mg Mn/m<sup>3</sup>.”

Looking back, I note that use of both soluble Mn and minimally adverse effects are conservative choices as a basis of acute toxicity factors.

I hope this helps further any continuing conversations about this important subject. Have a great day.

Sincerely,

Joseph “Kip” Haney, MS  
TCEQ  
Toxicology Division

**Appendix Q: DEQ and OHA 2024  
Memorandum on the DEQ Toxicity  
Reference Value Proposal for 24-hour  
Acute Inhalation Exposure to  
Manganese**





# Memorandum

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**To:** Ali Mirzakhali, DEQ Air Quality Administrator

**CC:** JR Giska, DEQ Cleaner Air Oregon Program Manager

**From:** Cleaner Air Oregon Toxicology Team

- Holly Dixon, Oregon Health Authority (OHA) Public Health Toxicologist
- David Farrer, OHA Public Health Toxicologist
- Mike Poulsen, DEQ Toxicologist
- Susan MacMillan, DEQ Air Toxics Science & Policy Analyst

**Date:** July 26, 2024

**Subject:** DEQ Toxicity Reference Value (TRV) Proposal for 24-hour Acute Inhalation Exposure to Manganese

## 1. Key Takeaway

DEQ proposes that the DEQ toxicity reference value (TRV) for 24-hour acute inhalation exposure to manganese should be changed from 0.3  $\mu\text{g}/\text{m}^3$  to 1.3  $\mu\text{g}/\text{m}^3$ .

## 2. Background Information

### 2.1. Current DEQ TRV

DEQ's existing TRV for 24-hour acute inhalation exposure to manganese is 0.3  $\mu\text{g}/\text{m}^3$ . Hereafter, the acute manganese TRV is referred to as the "acute TRV". A TRV is the concentration of a toxic air contaminant below which it is unlikely to cause health problems when inhaled. The existing acute TRV is based on a chronic exposure TRV from CalEPA's Office of Environmental Health and Hazard Assessment (OEHHA). The existing TRV is based on a study that reported neurotoxicity in workers exposed to manganese for an average of 5.3 years and up to 17 years (Roels et al., 1992). DEQ would prefer to derive an acute TRV from a study with an acute exposure duration. In cases where chronic exposure studies are used to derive an acute exposure TRV, DEQ stated in the [TRV update fact sheet](#) that DEQ and Oregon Health Authority (OHA) would prioritize finding alternative TRVs that are based on studies with acute exposure periods during the TRV review.

### 2.2. Current TRV Review and Manganese Petition

DEQ and OHA are currently reviewing the inhalation TRVs used in DEQ's air quality programs. Existing TRVs are in Oregon Administrative Rule (OAR, [340-247-8010 Table 2](#)). As part of the TRV review process, DEQ OARs give an option for members of the public to [submit petitions](#) to suggest TRV updates. DEQ welcomed petitions for consideration during the current TRV update process. Petitions were due in late 2022.

DEQ received one petition to change DEQ's acute manganese TRV (Bridgewater Group, 2022). The petition was prepared by Bridgewater Group, a consulting firm that works extensively with sources in Oregon on air quality permitting actions, including Cleaner Air Oregon Risk



# Memorandum

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Assessments. The toxicological information and analysis for the petition was provided by ToxStrategies, a scientific consulting firm that provides information to address regulatory issues. The petition proposes to increase the DEQ acute manganese TRV from  $0.3 \mu\text{g}/\text{m}^3$  to  $5 \mu\text{g}/\text{m}^3$ , which is consistent with the 24-hour reference value (ReV) developed by the Texas Commission on Environmental Quality (TCEQ, 2017). While the TRV proposed by Bridgewater Group is equivalent to the TCEQ TRV, the Bridgewater Group petition proposed a different set of uncertainty factors (UFs) in its derivation than the ones used by TCEQ.

Staff at ToxStrategies published a peer-reviewed manuscript titled “Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese” in *Regulatory Toxicology and Pharmacology* (Perry et al., 2023); hereafter, referred to as “Perry et al.”. The Perry et al. manuscript states that the work was supported by Gunderson LLC, of Portland, OR and Cascade Steel Rolling Mills, Inc., of McMinnville, OR. Similar to the Bridgewater Group petition, the acute TRV proposed by Perry et al. for manganese is equivalent to the TCEQ TRV; however, Perry et al. proposes a different set of uncertainty factors compared to TCEQ and the Bridgewater Group petition.

The similarities and differences between the Bridgewater Group petition, TCEQ, and Perry et al. are discussed in detail in [this DEQ framing document](#) that was written by DEQ and OHA to prepare the Air Toxics Science Advisory Committee (ATSAC) for a discussion on potentially changing DEQ’s acute TRV. For more information about the purpose of ATSAC and background of ATSAC members, refer to [this DEQ website](#).

## 2.3. ATSAC Member Feedback on the Petition

DEQ and a third-party meeting facilitator, Kearns & West, held an ATSAC meeting on **April 3, 2024**, to gather feedback from ATSAC members on the Bridgewater Group petition. ATSAC members were asked to read the petition, the Perry et al. manuscript, and DEQ’s framing document, and also prepare answers to DEQ’s discussion questions in advance of the meeting. ToxStrategies as well as DEQ and OHA staff gave presentations during the meeting. During the meeting, ATSAC members discussed each component of deriving an acute TRV given the key studies used by the Bridgewater Group petition, TCEQ, and Perry et al. DEQ did not develop an acute TRV proposal in advance of the ATSAC meeting. ATSAC member feedback from the meeting was used to inform the TRV proposal that is in this memorandum. **ATSAC meeting minutes are available [here](#) and a video recording is available [here](#).**

Following the April 3, 2024 ATSAC meeting, Bridgewater Group, ToxStrategies, and TCEQ provided additional documents and information which were shared with ATSAC as follows:

- **April 8, 2024:** ToxStrategies sent DEQ additional information related to some of the ATSAC questions asked during the April 3 meeting ([document linked here](#)).
- **April 9, 2024:** Joseph Haney in the Toxicology Division at TCEQ emailed OHA additional information about exposure duration adjustments ([email linked here](#)).
- **April 12, 2024:** DEQ shared the additional information sent by ToxStrategies and TCEQ on April 8 and April 9 with ATSAC and asked ATSAC three follow-up questions via email.

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The email DEQ sent to ATSAC as well as the compiled ATSAC feedback is available in [this document](#).

- **May 7, 2024:** Bridgewater Group sent DEQ an additional report from ToxStrategies regarding the time adjustment factor to the acute TRV ([email and report linked here](#)).
- **May 15, 2024:** DEQ shared the additional information sent by Bridgewater Group on May 7 with ATSAC and asked if ATSAC opinions had changed due to the new information. The email DEQ sent to ATSAC as well as compiled ATSAC feedback is available in [this email thread](#). DEQ also compiled ATSAC members' TRV derivation worksheets in [this document](#) and sent to ATSAC. To date, no ATSAC members have requested any changes to their TRV derivation worksheets.

## 3. TRV Proposal

The Cleaner Air Oregon toxicology team considered the acute TRV information received from the Bridgewater Group and ATSAC. Hereafter, the Cleaner Air Oregon toxicology team will be referred to as "DEQ". DEQ proposes the following derivation for DEQ's 24-hour acute inhalation exposure manganese TRV (Table 1).

**Table 1.** DEQ's proposed derivation of the 24-hour acute manganese TRV.

| Parameter                                          | Summary                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Key Studies                                        | Dorman et al. (2005) and Erikson et al. (2008)                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Study Population                                   | Male Rhesus Monkeys (20-24 months)                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Exposure Method                                    | Inhalation of MnSO <sub>4</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Exposure Continuity                                | 6 hours/day, 5 days/week                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Exposure Duration                                  | 15 exposure days                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Critical Effects                                   | <p>Dorman et al. 2005</p> <ul style="list-style-type: none"> <li>• Respiratory system</li> <li>• Inflammatory airway changes (e.g., mild bronchiolitis, alveolar duct inflammation)</li> </ul> <p>Erikson et al. 2008</p> <ul style="list-style-type: none"> <li>• Nervous system</li> <li>• Biochemical markers of oxidative stress in the brain (decreased glutathione levels and reversible increased glutamine synthetase protein with decreased gene expression)</li> </ul> |
| Point of Departure (POD)                           | 1.5 mg/m <sup>3</sup> ; lowest observed adverse effect level (LOAEL)                                                                                                                                                                                                                                                                                                                                                                                                             |
| Time Adjusted Exposure                             | 0.375 mg/m <sup>3</sup> [=1.5 mg/m <sup>3</sup> x (6 hr/24 hr)]                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Human Equivalent Concentration                     | 0.375 mg/m <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Interspecies Uncertainty Factor (UF <sub>A</sub> ) | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Intraspecies Uncertainty Factor (UF <sub>H</sub> ) | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| LOAEL Uncertainty Factor (UF <sub>L</sub> )        | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Subchronic Uncertainty Factor (UF <sub>S</sub> )   | NA                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |



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| Parameter                                      | Summary                                                          |
|------------------------------------------------|------------------------------------------------------------------|
| Database Uncertainty Factor (UF <sub>D</sub> ) | 3                                                                |
| Total Uncertainty Factor                       | 300 (=3x10x3x3)                                                  |
| <b>24-hour Acute Manganese TRV</b>             | <b>1.3 µg/m<sup>3</sup> (rounded from 1.25 µg/m<sup>3</sup>)</b> |

## 3.1. Key Studies and Point of Departure (POD)

DEQ proposes to use the same two key studies (Dorman et al. 2005 and Erikson et al. 2008) that are used in Perry et al. Both studies have the same POD, a lowest observed adverse effect level (LOAEL) of 1.5 µg/m<sup>3</sup>. DEQ agrees with the Bridgewater Group that these two key studies are a good resource for developing a new DEQ acute TRV for three primary reasons:

1. The exposure durations in these studies are much closer to DEQ's definition of acute exposure than the key study used in DEQ's current acute TRV. The average exposure time is 5.3 years in Roels et al. (1992), the key study currently being used by DEQ for an acute TRV.
2. The study populations are monkeys rather than other animal models (such as rodents) that are less similar to humans.
3. The manganese exposures and particle size are well characterized.

DEQ acknowledges that Dorman et al. 2005 and Erikson et al. 2008 also have limitations. Examples of limitations include:

- Both key studies are small, with around 4-6 monkeys per exposure group.
- Both key studies looked at limited exposure concentrations and endpoints.
- As described further in Section 3.8 below, DEQ's authoritative sources (the Agency for Toxic Substances and Disease Registry (ATSDR) and OEHHA) decided not to derive an acute toxicity value after a comprehensive review of all available toxicity information. The Dorman et al. 2005 study was available during ATSDR's and OEHHA's reviews and it is cited in both of those organization's derivation documents.

ATSAC members provided feedback on deriving a proposed DEQ acute TRV using both Dorman et al. 2005 and Erikson et al. 2008 (e.g., [compiled ATSAC worksheets](#)). Generally, ATSAC members were supportive of using Dorman et al. 2005 and Erikson et al. 2008 as the key studies for deriving a new DEQ acute TRV. ATSAC members also highlighted study limitations. For example, John Budroe stated that "Dorman 2005 and Erikson 2008 are not especially good studies; these studies have a freestanding LOAEL with no controls" (DEQ, 2024a). In addition, here is an excerpt from the meeting minutes describing ATSAC member Daisy Dong's comments:

"Daisy agreed with combining both studies (Dorman et al. 2005 and Erikson et al. 2008). Daisy notes that a major limitation of these studies is that they have one dose. She said that if DEQ has to come up with an acute TRV, and if the other options are to not have an acute TRV at all or to adapt a chronic TRV, she prefers using the two critical studies in Table 1 (Dorman et al. 2005 and Erikson et al. 2008). The primate studies are preferable over the rat studies due to their greater relevance to humans. The combination of the two

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critical studies also gives us more information for a regulatory toxicity value than only gene expression or protein level data.” (DEQ, 2024a).

Overall, DEQ proposes using both Dorman et al. 2005 and Erikson et al. 2008 to derive a DEQ acute TRV rather than DEQ’s current approach of using a key study with a chronic exposure duration.

## 3.2. Time Adjustment

DEQ proposes to apply an exposure time adjustment since the monkeys in the key studies were exposed 6 hours/day, 5 days/week for 15 exposure days, whereas the 24-hour TRV is designed to protect against a daily exposure.

DEQ proposes to multiply the POD concentration by 6 hours/24 hours to adjust the intermittent exposure regimen in the key studies to a continuous 24-hour TRV:

$$\begin{aligned} \text{24-hour Time Adjusted POD} &= \text{POD} \times \frac{6 \text{ hours}}{24 \text{ hours}} && (\text{Eq. 1}) \\ &= 1.5 \text{ mg/m}^3 \times 0.25 \\ &= 0.375 \text{ mg/m}^3 \end{aligned}$$

The Bridgewater Group petition, TCEQ, and Perry et al. did not include a time adjustment in the derivation of their acute TRVs. In contrast, all ATSAC members supported a time adjustment to account for adjusting the exposure duration from 6 hours/day in the key studies to a 24-hour TRV. After additional information was provided by Bridgewater Group, ToxStrategies and TCEQ on this issue, no ATSAC members requested any changes to their prior recommendation.

Two ATSAC members responded to DEQ after DEQ sent ATSAC the May 7 ToxStrategies report on the time adjustment. Both ATSAC members continued to support the addition of the time adjustment and DEQ agrees with their reasoning. For example, ATSAC member Daisy Dong stated:

“The additional information [from ToxStrategies] only addressed the pharmacokinetic (PK) difference but not the pharmacodynamic (PD) difference between the continuous 24h exposure and the 6hr/d, 5d/wk for 3 weeks exposure. As I commented earlier, only when both PK **AND** PD indicate no differences between these two exposure scenarios, then it is ok not to do time adjustment. Therefore, my opinion stays same as before.” –  
Source: [ATSAC Email Responses to Petitioner Supplemental Information, May 22, 2024](#)

Pharmacokinetics (PK) and toxicokinetics (TK) are terms that are used interchangeably in many situations, as in the case of the ATSAC quote above and other places in this memorandum. This is also the case for pharmacodynamics (PD) and toxicodynamics (TD). Briefly, TK describes toxic contaminant uptake, internal distribution, biotransformation, and elimination in an organism; i.e., what an organism does with a toxic contaminant like manganese (Ashauer & Escher, 2010). TD



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describes what the toxic contaminant does to the organism, which can include information on the time course of toxic action at the target site, physiological impairment of the organism, and emergence of toxic effects such as mortality (Ashauer & Escher, 2010). TK is termed PK in pharmacology and TD is termed PD in pharmacology; these terms in pharmacology reference a therapeutic drug instead of a toxic contaminant.

ATSAC member John Stanek also brought up an observation that while TCEQ's 24-hour toxicity value does not use a time adjustment, TCEQ's 1-hour toxicity value based on the same key study (Dorman et al. 2005) uses a time adjustment based on Haber's rule as modified by ten Berge et al.:

"I found it interesting as cited in Table 1 of Perry that TCEQ applied a modified (ten Berge) Cxt to calculate a 1-hr value (using the same Dorman study LOAEL of 1.5 mg/m<sup>3</sup> for respiratory effects). However, they determined not to apply it to extrapolate to 24-hrs – this appears methodologically inconsistent to me and is the one of the bases for this issue."  
– Source: [ATSAC Email Responses to Petitioner Supplemental Information, May 22, 2024](#)

TCEQ's *Guidelines to Develop Toxicity Factors* covers TCEQ's default approaches for time adjustments (section 4.6.2.4.1.2):

"When a chemical's MOA is poorly characterized, the C exponent, "n" (see Section 3.8 regarding Haber's rule,  $C^n \times T = K$ ), is set equal to a default value of 1, which is considered to be conservative when performing a duration adjustment from a shorter exposure duration to a longer one." (TCEQ, 2015).

TCEQ used n=3 in the modified (ten Berge) Haber's rule equation above for their 1-hour toxicity value based off Dorman et al. 2005. The n=3 is TCEQ's default assumption when going from a longer exposure period to shorter exposure toxicity value. Here, DEQ is taking a shorter exposure period from Dorman et al. 2005 and Erikson et al. 2008 (6 hours/day) and applying that exposure to a longer 24-hour TRV. With the information available in the key studies, DEQ agrees with a n=1 for Haber's rule, which is equivalent to the time adjusted POD proposed in Eq. 1.

### 3.3. Adjustment from Animal-to-Human Exposure

DEQ proposes to use a regional deposited dose ratio (RDDR) of 1 due to the similarities in lung anatomy between rhesus monkeys and humans. For example, Perry et al. states:

"Dorman et al. (2005) discussed the similarities of monkey and human respiratory-tract anatomy, stating that, based on the Asgharian et al. (1995) model, a particle size of 1.5  $\mu\text{m}$  (near the 1.72- to 2.12- $\mu\text{m}$  range used by Dorman et al. (2005)) predicted approximately equal pulmonary deposition efficiency of 35% in both humans and rhesus monkeys. Therefore, no dosimetric adjustment is required when using these data to assess exposures in humans. Further, Campbell et al. (2023) demonstrated that the rate





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constants for binding and cellular uptake established in monkeys are applicable to humans.” (2023).

To derive the Human Equivalent Concentration POD in Table 1, the Time Adjusted POD was multiplied by the RDDR of 1:

$$\begin{aligned} \text{24-hour Human Equivalent Concentration} &= \text{Time Adjusted POD} \times \text{RDDR} && (\text{Eq. 2}) \\ &= 0.375 \text{ mg/m}^3 \times 1 \\ &= 0.375 \text{ mg/m}^3 \end{aligned}$$

No ATSAC member suggested a different adjustment for animal-to-human exposure. Compiled ATSAC feedback indicates that all ATSAC members agreed that no additional adjustment is needed to calculate the Human Equivalent Concentration.

### 3.4. Interspecies Uncertainty Factor ( $UF_A$ )

A  $UF_A$  is used to account for the uncertainty in extrapolating laboratory animal data to humans (U.S. EPA, 1994). The study population in the two key studies are non-human primates (rhesus monkeys), so DEQ selected a  **$UF_A$  of 3**. If the key studies had been human studies, DEQ would have selected a  $UF_A$  of 1. The respiratory and nervous systems are very similar between humans and rhesus monkeys, which is why DEQ chose a  $UF_A$  of 3 instead of 10. The similarities in the respiratory system are noted in Section 3.3 above. The similarities in the nervous system are noted in Perry et al.:

“We consider monkeys to be a preferable human model to rats, due to their similarities to humans in Mn [manganese] brain accumulation distribution patterns, neurological signs, and nose/brain anatomy and physiology (Burton and Guilarte, 2009; Newland, 1999; Dorman et al., 2006). Further, unlike rodents, nonhuman primates largely replicate the neurotoxic effects of Mn observed in humans (Dorman, 2023)” (2023).

Compiled ATSAC feedback indicates that all ATSAC members are in support of a  $UF_A$  of 3 when using Dorman et al. 2005 and Erikson et al. 2008 as the key studies.

### 3.5. Intraspecies Uncertainty Factor ( $UF_H$ )

A  $UF_H$  is used to account for the variation in sensitivity among members of the human population (U.S. EPA, 1994). DEQ proposes a  **$UF_H$  of 10** to address DEQ’s concern that prenatal and young children may be more susceptible to manganese exposure due to toxicodynamic differences between developing children and adults. OEHHHA’s comprehensive manganese report highlights eight reasons why children may be more susceptible to manganese toxicity than adults (2008). Here are three examples from OEHHHA’s report:

1. “The newborn’s brain is still developing, myelination is incomplete, and the blood-brain barrier is not fully formed (Chan et al., 1992). These conditions facilitate manganese uptake into the central nervous system and increase the risk of attaining toxic levels.”



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2. "The liver of newborns has not yet developed the ability to maintain safe levels of manganese in the bloodstream and brain tissues by excreting excess manganese in the bile, i.e., homeostasis of manganese has not yet developed (Miller et al., 1975)."
3. "Manganese exposures in childhood are associated with impaired neurodevelopment including decrements in intellectual function. Thus, a major toxicodynamic factor that differs between adults and children, namely development of the central nervous system, presents hypersensitive targets for toxicity in the developing infant and child."

Five of the six ATSAC members recommended a  $UF_H$  of 10 and one recommended a  $UF_H$  of 30 (included an additional subfactor of 3 to adjust for residual pharmacokinetic differences they did not think were accounted for by the petitioner's PBPK modeling). For context, UFs are generally 3- to 10-fold factors (U.S. EPA, 1994). OEHHHA toxicity values can have  $UF_H$ s of up to 100, but 10 is usually the maximum  $UF_H$  for DEQ's other authoritative sources (EPA and ATSDR). A comparison of UFs used by different organizations is in Appendix A of DEQ's Manganese Framing Document (DEQ, 2024b).

## 3.6. LOAEL to NOAEL Uncertainty Factor ( $UF_L$ )

A  $UF_L$  is used to account for the uncertainty in using LOAEL data rather than no observed adverse effect level (NOAEL) data for the POD (U.S. EPA, 1994). DEQ proposes a  **$UF_L$  of 3** because, although a NOAEL was not available, most critical effects in the key studies were reported to be mild and reversible (Table 1). For example, Dorman et al. and Erikson et al. state:

- "High-dose subchronic manganese sulfate inhalation is associated with increased lung manganese concentrations, mild subacute bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue. Bronchiolitis and alveolar duct inflammatory changes were absent 45 days post-exposure, suggesting that these lesions are reversible upon cessation of subchronic high-dose manganese exposure. These small airway changes occurred in the absence of observable clinical signs." (Dorman et al., 2005).
- "Overall, the nonhuman primate brain responds to airborne Mn in a heterogeneous manner and most alterations in these biomarkers of neurotoxicity are reversible upon cessation of Mn exposure." (Erikson et al., 2008).

DEQ's proposal of a  $UF_L$  of 3 is in line with two of DEQ's authoritative sources. For example, ATSDR uses a  $UF_L$  of 3 when the LOAEL has minimal effects and OEHHHA uses a  $UF_L$  of 6 when the LOAEL has mild effects (DEQ, 2024b). A  $UF_L$  of 1 is not warranted because a NOAEL is not available in the key studies.

Perry et al. and three ATSAC members were in support of a  $UF_L$  of 10. ATSAC statements included:

- "It is worth to mention that a LOAEL to NOAEL of 10 is not overly conservative given that the critical effects include neurotoxicity and many brain neurotoxicity biomarkers did





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change at the LOAEL in monkeys.” – ATSAC member Daisy Dong ([DEQ and ATSAC Email Communication 4-26-2024](#))

- “A full UF for LOAEL is likely warranted as there is not a defined NOAEL under similar exposure conditions (without making a few assumptions).” – ATSAC member John Stanek ([Compiled ATSAC Manganese TRV Worksheets](#))

The other three ATSAC members had similar opinions and suggested  $UF_L$ s of 2, 3, and 6. ATSAC member Susan Tilton stated, “I recommend an extrapolation of 2-fold since the observed pulmonary pathology was characterized as mild/minor and reversible.” ATSAC member John Budroe picked a 6 because the LOAEL is a mild effect, and this qualifies as a  $UF_L$  of 6 following OEHHHA guidance. Another ATSAC member did not propose a final  $UF_L$ , but stated he wondered if more work could be done to further explore reducing the  $UF_L$ .

Overall, DEQ did not think a  $UF_L$  of 10 was warranted given that most of the critical effects for the LOAEL were characterized as mild and reversible. DEQ acknowledges that not all the neurotoxicity biomarkers in Erickson et al. were observed to be reversible during the timeframe of the study. DEQ looked at the totality of information available in both key studies to decide to choose a reduced  $UF_L$ . In addition, while DEQ contemplated each UF individually, DEQ did consider the interplay between the  $UF_L$  and  $UF_D$  and thinks that these UFs are closely related. The product of both the  $UF_L$  and  $UF_D$  was similar across all ATSAC members (refer to section 3.9; i.e., ATSAC members that selected a  $UF_L$  of 10 then selected a  $UF_D$  of 1 and ATSAC members that selected a reduced  $UF_L$  then selected a  $UF_D$  of 3). With both the  $UF_L$  and  $UF_D$ , DEQ is building in a safety buffer to protect against the potential of neurodevelopmental effects in sensitive populations given limited toxicological information.

## 3.7. Subchronic Uncertainty Factor ( $UF_S$ )

A  $UF_S$  is not applicable. A  $UF_S$  is only for extrapolating subchronic exposure durations to chronic TRVs, and not for extrapolating subchronic exposure durations to acute TRVs.

## 3.8. Database Uncertainty Factor ( $UF_D$ )

A  $UF_D$  is used to account for the inability of a single study (or two) to adequately address all possible adverse human health outcomes (U.S. EPA, 1994). DEQ proposes a  **$UF_D$  of 3** to address DEQ’s concern about the lack of studies on the impact of manganese on the developing nervous system.

Other organizations that have done comprehensive reviews on the available manganese toxicology database have commented on the lack of information.

**ATSDR.** As ATSAC member John Budroe pointed out, ATSDR’s 2012 Manganese Toxicological Profile stated that the available data on the toxicity of inhaled manganese was considered insufficient for deriving an acute or intermediate duration inhalation toxicity value (ATSDR, 2012; DEQ, 2024a). ATSDR’s toxicological profile also has a section on physiologically based pharmacokinetic (PBPK) and pharmacodynamic (PD) models (section 3.4.5 of ATSDR’s Tox Profile). However, ATSDR does not use the PBPK and PBPD models to inform an acute or

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intermediate duration toxicity value. David Dorman, the first author of one of the key studies in the TRV proposal in this memorandum, was one of three peer reviewers of the ATSDR Manganese Toxicological Profile, which implies he had the opportunity to comment on and review ATSDR's decision to not derive toxicity values for acute or intermediate duration inhalation exposures.

**OEHHA.** OEHHA did not develop an acute exposure TRV for manganese in their 2008 report because “the database is insufficient” (OEHHA, 2008). The Dorman et al. 2005 study was available during OEHHA's review and is referenced in the report. OEHHA provided information on why the potential for developmental neurological issues from manganese is a concern (OEHHA, 2008). OEHHA stated that several epidemiology studies have reported correlations between early life exposure to excessive manganese and symptoms of impaired neurodevelopment as revealed on neurobehavioral tests and in poorer academic performance (OEHHA, 2008). For example, in a prospective study of the neurobehavioral effects of in utero exposure to manganese, Takser et al. reported an inverse correlation between cord blood manganese at birth and three subscales of psychomotor development (attention, nonverbal memory, and hand skills) measured at three years of age (OEHHA, 2008; 2003).

**TCEQ.** TCEQ used the Dorman et al. 2005 study to derive an acute TRV. They used a  $UF_D$  of 6 in their derivation. TCEQ states, “These database limitations result in a low confidence in the acute/subacute database overall (TCEQ 2015), consistent with ATSDR (2012) not deriving an acute duration minimal risk level (MRL) (inhalation or oral)” (2017). TCEQ also comments, “additional studies involving neurobehavioral effects following gestational and postnatal exposure to airborne Mn are necessary. The addition of developmental neurotoxicology studies using a functional observational battery design and a wide range of well-established measures would result in a more complete inhalation (and oral) database” (2017).

Three ATSAC members suggested a  $UF_D$  of 3, mentioning this UF is needed to reflect the lack of neurobehavioral development data. Three ATSAC members suggested a  $UF_D$  of 1 and expressed confidence in the Bridgewater Group's PBPK modeling. ATSAC member Daisy Dong recommended a  $UF_D$  of 1 and stated that these manganese PBPK models, compared to other chemicals, are actually quite good and included many different variables such as diet contribution and different manganese forms (DEQ, 2024a).

Overall, DEQ did not think that a  $UF_D$  of 1 was adequate given the information from ATSDR, OEHHA, and TCEQ on the lack of a complete database. DEQ also did not think a  $UF_D$  of 10 was warranted given that no ATSAC members suggested a  $UF_D$  of 10 and half of the ATSAC members suggested a  $UF_D$  of 1. DEQ chose a  $UF_D$  of 3 for the final proposal, which aligned with the other half of the ATSAC members.

## 3.9. Total UF

The proposed UFs differed between ATSAC members and organizations (Figure 1). A range of UF proposals was expected; uncertainty is inherent in deriving TRVs and strategies for quantifying uncertainty differ between toxicologists as well as organizations that set TRVs. However, even though there was a range of UF proposals, trends emerged as mentioned in the subsections

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above and seen in Figure 1. DEQ's proposal incorporates these trends and reflects DEQ's health protective approach to scientific uncertainty.

**Figure 1.** Comparison of the proposed UFs and TRV between the six ATSAC members, TCEQ, the Bridgewater Group petition, Perry et al., and DEQ. The size of each bar is scaled to the range for each column.

|                            | UF-A | UF-H | UF-L | UF-D | Total UF | TRV (ug/m3) |
|----------------------------|------|------|------|------|----------|-------------|
| John Vandenberg, ATSAC     | 3    | 10   | 3    | 3    | 300      | 1.3         |
| Daisy Dong, ATSAC          | 3    | 10   | 10   | 1    | 300      | 1.3         |
| Susan Tilton, ATSAC        | 3    | 10   | 2    | 3    | 180      | 2.1         |
| John Budroe, ATSAC         | 3    | 30   | 6    | 3    | 1600     | 0.2         |
| Jefferson Fowles, ATSAC    | 3    | 10   | 10   | 1    | 300      | 1.3         |
| John Stanek, ATSAC         | 3    | 10   | 10   | 1    | 300      | 1.3         |
| TCEQ                       | 3    | 10   | 2    | 6    | 300      | 5           |
| Bridgewater Group Petition | 10   | 10   | 3    | 1    | 300      | 5           |
| Perry et al. 2023          | 3    | 10   | 10   | 1    | 300      | 5           |
| DEQ Proposal               | 3    | 10   | 3    | 3    | 300      | 1.3         |

Source: Oregon DEQ 2024 • Created with Datawrapper

DEQ proposes a total UF of 300 as calculated below:

$$\begin{aligned}
 \text{Total UF} &= \text{UF}_A \times \text{UF}_H \times \text{UF}_L \times \text{UF}_D \\
 &= 3 \times 10 \times 3 \times 3 \\
 &= 300 \text{ (rounded to one significant figure)}
 \end{aligned}
 \tag{Eq. 3}$$

Four of the six ATSAC members suggested a total UF of 300, which is equivalent to the DEQ proposal. ATSAC members suggested total UFs ranging from 180 to 1600 (Figure 1).

## 3.10. TRV Proposal and Conclusion

DEQ proposes that the DEQ TRV for 24-hour acute inhalation exposure to manganese should be  $1.3 \mu\text{g}/\text{m}^3$  (rounded from the calculated value of  $1.25 \mu\text{g}/\text{m}^3$ ):

$$\begin{aligned}
 \text{Proposed DEQ 24 – Hour Acute TRV} &= \text{Human Equivalent Concentration POD} \div \text{Total UF} \tag{Eq. 4} \\
 &= 0.375 \text{ mg}/\text{m}^3 \div 300 \\
 &= 0.00125 \text{ mg}/\text{m}^3 \\
 &= 1.3 \mu\text{g}/\text{m}^3 \text{ (rounded to two significant figures)}
 \end{aligned}$$

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DEQ's priority when deriving this TRV was to make sure that the TRV protects the health of vulnerable populations, such as children during critical developmental windows. DEQ's proposal is also equivalent to the TRV proposals from four of the six ATSAC members (Table 2). ATSAC member TRV proposals ranged from 0.2 to 1.3  $\mu\text{g}/\text{m}^3$  (Table 2).

**Table 2.** Comparison of proposed derivation information between TCEQ, the Bridgewater Group petition, Perry et al., ATSAC members, and DEQ for a 24-hour acute manganese TRV.

|                            | Time Adjust.? | Human Equiv. Conc. Adjust.? | Uncertainty Factor (UF)       |                               |                       |                             |                           |             | TRV ( $\mu\text{g}/\text{m}^3$ ) |
|----------------------------|---------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|-----------------------------|---------------------------|-------------|----------------------------------|
|                            |               |                             | UF <sub>A</sub> Inter-species | UF <sub>H</sub> Intra-species | UF <sub>L</sub> LOAEL | UF <sub>S</sub> Sub-chronic | UF <sub>D</sub> Data base | Total UF    |                                  |
| TCEQ                       | No            | No                          | 3                             | 10                            | 2                     | NA                          | 6                         | 300*        | 5.0                              |
| Bridgewater Group Petition | No            | No                          | 10                            | 10                            | 3                     | NA                          | 1                         | 300         | 5.0                              |
| Perry et al. 2023          | No            | No                          | 3                             | 10                            | 10                    | NA                          | 1                         | 300         | 5.0                              |
| Range from ATSAC Members   | Yes           | No                          | 3                             | 10 to 30                      | 2 to 10               | NA                          | 1 to 3                    | 180 to 1600 | 0.2 to 1.3                       |
| <b>DEQ Proposal</b>        | <b>Yes</b>    | <b>No</b>                   | <b>3</b>                      | <b>10</b>                     | <b>3</b>              | <b>NA</b>                   | <b>3</b>                  | <b>300</b>  | <b>1.3</b>                       |

\*While the total UF is equivalent to 360, TCEQ used a total UF of 300 when calculating the TRV. TCEQ has a policy that 300 is the maximum total UF allowed for acute TRVs.

To put this acute TRV in context of DEQ's other TRV for manganese inhalation exposure, DEQ's 2018 chronic noncancer TRV for manganese is 0.09  $\mu\text{g}/\text{m}^3$  (OEHHA value adopted by a previous ATSAC). DEQ is not proposing to change this chronic noncancer TRV in the current TRV review. There is no cancer TRV available for manganese.

## References

- Ashauer, R., & Escher, B. I. (2010). Advantages of toxicokinetic and toxicodynamic modelling in aquatic ecotoxicology and risk assessment. *Journal of Environmental Monitoring*, 12(11), 2056–2061.
- ATSDR. (2012). *Toxicological Profile for Manganese*. Agency for Toxic Substances and Disease Registry (ATSDR). <https://www.atsdr.cdc.gov/ToxProfiles/tp151.pdf>
- Bridgewater Group. (2022). *Supporting Evidence for Petition for Oregon Department of Environmental Quality (ODEQ) Air Toxics Review to Revise the Acute Toxicity Reference Value (TRV) for Acute Manganese Exposure*. <https://www.oregon.gov/deq/daq/cao/Documents/CAOToxPetition.pdf>

# Memorandum

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- DEQ. (2024a). *Air Toxics Science Advisory Committee (ATSAC) Meeting 3 Minutes: April 3, 2024*. Oregon Department of Environmental Quality.  
<https://www.oregon.gov/deq/eq/Documents/ATSAC-20240403MSummary.pdf>
- DEQ. (2024b). *Framing document for DEQ's Air Toxics Science Advisory Committee: Petition for changes for DEQ's manganese toxicity reference value for acute exposure*. Oregon Department of Environmental Quality.  
<https://www.oregon.gov/deq/eq/Documents/ATSAC-ManganesePetition.pdf>
- Dorman, D. C., Struve, M. F., Gross, E. A., Wong, B. A., & Howroyd, P. C. (2005). Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. *Respiratory Research*, 6(1), Article 1.
- Erikson, K. M., Dorman, D. C., Lash, L. H., & Aschner, M. (2008). Duration of airborne-manganese exposure in rhesus monkeys is associated with brain regional changes in biomarkers of neurotoxicity. *Neurotoxicology*, 29(3), Article 3.
- OEHHA. (2008). *Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries: Manganese and Compounds Reference Exposure Levels*. CalEPA Office of Environmental Health Hazard Assessment (OEHHA).  
<https://oehha.ca.gov/media/downloads/crnrr/appendixd1final.pdf>
- Perry, C. S., Blanchette, A. D., Vivanco, S. N., Verwiell, A. H., & Proctor, D. M. (2023). Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese. *Regulatory Toxicology and Pharmacology*, 145, 105518.
- Roels, H., Ghyselen, P., Buchet, J.-P., Ceulemans, E., & Lauwerys, R. (1992). Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *British Journal of Industrial Medicine*, 49(1), Article 1.
- Takser, L., Mergler, D., Hellier, G., Sahuquillo, J., & Huel, G. (2003). Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology*, 24(4–5), Article 4–5.
- TCEQ. (2015). *TCEQ Guidelines to Develop Toxicity Factors*. RG-442: Toxicology Division of the Texas Commission on Environmental Quality (TCEQ).  
<https://www.tceq.texas.gov/downloads/toxicology/publications/rg-442.pdf>
- TCEQ. (2017). *Development Support Document: Manganese and Inorganic Manganese Compounds*. Texas Commission on Environmental Quality (TCEQ).  
<https://www.tceq.texas.gov/downloads/toxicology/dsd/final/mn.pdf>
- U.S. EPA. (1994). *Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry*. U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC, EPA/600/8-90/066F.  
<https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993>



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**Appendix R: ATSAC Email Exchanges  
on brominated dioxins and furans, 1-  
methylnaphthalene, and  
perfluorodecanoic acid (PFDA)**





Oregon Department of Environmental Quality

# Compilation of ATSAC Responses to TEFs & Brominated Analogues Email on 11-1-2023

## Copy of DEQ Email

**From:** GOECKNER Apollonia \* DEQ

**Sent:** Wednesday, November 1, 2023 11:30 AM

**To:** Budroe, John@OEHA <[john.budroe@oeha.ca.gov](mailto:john.budroe@oeha.ca.gov)>; Dong, Qiaoxiang@CDPR <[Qiaoxiang.Dong@cdpr.ca.gov](mailto:Qiaoxiang.Dong@cdpr.ca.gov)>; Jeff Fowles <[jfowles101@gmail.com](mailto:jfowles101@gmail.com)>; Stanek, John <[Stanek.John@epa.gov](mailto:Stanek.John@epa.gov)>; Tilton, Susan C <[susan.tilton@oregonstate.edu](mailto:susan.tilton@oregonstate.edu)>; John Vandenberg, Ph.D. <[john.vandenberg@duke.edu](mailto:john.vandenberg@duke.edu)>

**Cc:** GSKA JR \* DEQ <[JR.GSKA@deq.oregon.gov](mailto:JR.GSKA@deq.oregon.gov)>; Farrer David G <[DAVID.G.FARRER@oha.oregon.gov](mailto:DAVID.G.FARRER@oha.oregon.gov)>; Holly Dixon <[Holly.M.Dixon@oha.oregon.gov](mailto:Holly.M.Dixon@oha.oregon.gov)>; MACMILLAN Susan \* DEQ <[Susan.MACMILLAN@deq.oregon.gov](mailto:Susan.MACMILLAN@deq.oregon.gov)>; Ben Duncan <[bDuncan@kearnswest.com](mailto:bDuncan@kearnswest.com)>; Angela Hessenius <[AHessenius@kearnswest.com](mailto:AHessenius@kearnswest.com)>

**Subject:** Application of toxic equivalency factors (TEFs) for dioxins, furans, and dioxin-like PCB congeners to their brominated analogues

Dear ATSAC,

It has been a little over a month since our last communication with you. We hope you are well and had a good summer (or winter as per your relevant hemisphere).

We are still months away from scheduling a meeting for formal review of our Toxicity Reference Value (TRV) updates; however, we have come across a question that we would like your input on before we finalize these updates. This question is more open-ended than we expect most of our questions for you to be. We hope to get your input on this issue via email without an actual meeting, although we could host a meeting to discuss if you feel this is too complicated to do via email.

The attached review paper, as we understand it, proposes to apply the toxic equivalency factors (TEFs) designed for assessing risk from polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs) to their brominated analogues.

Our questions to you are:

1. Do we correctly understand what they are recommending?
2. Is the reasoning applied by the authors of this review sound?
3. Does this paper provide a sufficiently robust evidence base to adopt their proposal?
4. Do you know of other studies/papers that either support or argue against these authors' proposal?
5. As far as we know, no other government agencies have implemented this proposal. Do you know of any?
6. In light of all of the above, would you recommend that we apply existing TEFs for dioxins, furans, and dioxin-like PCBs to their brominated analogues when calculating toxic equivalency quotients (TEQs) at facilities in Oregon?
7. Do you think we need to have a virtual meeting about this?

Here is some additional Oregon-specific context if it helps you think through this:

- Oregon has permitted facilities that may emit these substances – e.g., incinerators, scrap metal foundries using electric arc furnaces.
- The Cleaner Air Oregon program looks closely at all emissions from sources and in many cases requires source testing to obtain representative emissions data – there are current methods used for sampling the chlorine-substituted compounds that could be used for analyzing the bromine-substituted molecules.
- DEQ is committed to understanding potential health risks from toxic air contaminants and needs to ensure we are not excluding a potentially significant source of health risk.

If you could please get us your responses to these questions by **January 5, 2024** we would really appreciate it. Please reply all via email, and note that your responses will be part of the public record.

Please let us know if you have any additional questions or concerns.

Thank you!

-ATSAC Governance Team

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State of Oregon  
Department of Environmental Quality



## ATSAC Responses

| ATSAC Member                                   | ATSAC Member Responses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <p><b>Dr. John Vendenberg</b><br/>1-5-2024</p> | <p><b>Question 1:</b> The authors (van den berg et. al., 2013<sup>1</sup>) are recommending that Toxic Equivalency Factors be applied for brominated -dioxin, -furan and -biphenyl compounds in the same fashion as is generally done for chlorinated -dioxin, -furan and -biphenyl compounds. This is based on emerging, but limited, information available on the presence and mode of action of these brominated compounds and the similarity in many aspects to the chlorinated compounds.</p> <p><sup>1</sup> van den berg, M et al., Polybrominated dibenzo-p-dioxins, dibenzofurans, and biphenyls: inclusion in the Toxicity Equivalency Factor concept for dioxin-like compounds. Toxicological Sciences 133(2), 197-208 (2013).</p> <p><b>Question 2:</b> The authors are internationally renowned toxicology experts and they have carefully considered and documented the rationale underlying their recommendations. Their discussion of available information on kinetics, metabolism and toxicity is sound and the alignment in Figure 1 of the paper of the relative potency factors for PXDDs, PXDFs and dl-PXBs is very informative. I find their reasoning to be sound.</p> <p><b>Question 3:</b> I think this paper is part of the evidence base but to me a single paper is not typically sufficient to adopt a proposal. To adopt a proposal the body of relevant literature needs to be considered, with an understanding of the strengths and limitations of the totality of evidence. That said, the summary and evaluation of evidence described in van den berg (2013) for PBDD/PBDFs appears sufficient to conclude that the use of TEFs is now warranted (see also my response to questions 4 and 6). I'm not certain the evidence is sufficient for the dioxin-like PBBs.</p> <p><b>Question 4:</b> A limited search of the literature published since the 2013 publication by van den berg et al (2013) found there have been many studies published that evaluate the potential exposures to these brominated compounds. A literature search of peer reviewed publications based just on the keyword "PBDD" returned over 460 references from a wide range of journals. Based on my limited review of some of this literature I find most provide information on formation and occurrence/exposure of the compounds and relatively few on the mechanism of action that support the author's proposal. For example, the study by Budin et al, Chemosphere 263(2021) provides relevant new information on the mechanism of action of these compounds and</p> |

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|                                             | <p>concludes “like PCDD/Fs, PBDD/PBDFs are potent activators of the human AhR”.</p> <p>I did not conduct a systematic review of the literature and recommend that a more thorough evaluation focused on the available toxicological science be considered.</p> <p><b>Question 5:</b> I’m not aware of any other agencies having implemented this proposal. I serve on the Secretary’s Science Advisory Board for the State of North Carolina and to my knowledge there are no NC standards or guidelines for PBDD/Fs. I do not find these brominated compounds listed as hazardous air pollutants under the current amendments to the Clean Air Act.</p> <p><b>Question 6:</b> I am inclined to conclude that the evidence is sufficient to apply TEFs for dioxins, furans and dioxin-like PCBs to their brominated analogues when calculating toxic equivalency quotients (TEQs) at facilities in Oregon, but I would prefer to have a discussion of this approach and hear from the other members of the ATSAC prior to making a final recommendation.</p> <p><b>Question 7:</b> Yes. A discussion as to what constitutes sufficient evidence to make a recommendation, and the specific information available on the brominated analogues to the chlorinated dioxins, furans and dioxin-like PCBs, would be useful.</p> |
| <p><b>Dr. Susan Tilton</b><br/>1-2-2024</p> | <p><b>Question 1:</b> Yes, as I understand it, this is still the current recommendation for polybrominated dibenzodioxins and dibenzofurans due to lack of data for brominated compounds.</p> <p><b>Questions 2 &amp; 3:</b> The rationale for use of TEFs for polybrominated dioxin-like compounds is because these compounds were found to function through the aryl hydrocarbon receptor to mediate toxicity similar to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and so can be compared to TCDD with a TEF = 1. Polychlorinated and polybrominated compounds also result in similar adverse outcomes. This is a reasonable approach in the absence of data for brominated analogues.</p> <p><b>Question 4:</b> In addition to the paper provided, there are papers that support use based on common mechanisms, common biological and toxic effects and similar potencies based on limited in vivo and in vitro data, but also some reports that note significant gaps observed in relative potencies between certain chlorinated and brominated dioxin congeners with substitutions at the same position. The WHO justifies use of TEFs based on the fact that any differences are likely within the</p>                                                                                                             |

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|                                                            | <p>assumed uncertainty of one order of magnitude for mammalian TEFs of chlorinated congeners. Therefore, using TEFs is worthwhile in the short-term so these compounds are included. In the long-term, values specific for brominated dioxins, furans and biphenyls should be developed.</p> <p>Hornung MW et al (1996) Toxic equivalency factors of polybrominated dibenzo-p-dioxin, dibenzofuran, biphenyl, and polyhalogenated diphenyl ether congeners based on rainbow trout early life stage mortality. <i>Toxicol. Appl. Pharmacol.</i> 140, 227–234.</p> <p>Nakayama K et al (2022) Determination of the relative potencies of brominated dioxins for risk assessment in aquatic environments using the early-life stage of Japanese medaka. <i>Ecotoxicol Environ Safety</i>. 247:114227.</p> <p>Olsman H et al (2009) Relative differences in aryl hydrocarbon receptor-mediated response for 18 polybrominated and mixed halogenated dibenzo-P-dioxins and -furans in cell lines from four different species. <i>Environ Toxicol Chem.</i> 26(11):2448-2454.</p> <p>Suzuki et al (2017) Dioxin-like activity of brominated dioxins as individual compounds or mixtures in in vitro reporter gene assays with rat and mouse hepatoma cell lines. <i>Toxicol In Vitro.</i> 44:134-141.</p> <p>Wall RJ et al (2015) Characterisation of chlorinated, brominated and mixed halogenated dioxins, furans and biphenyls as potent and as partial agonists of the Aryl hydrocarbon receptor. <i>Environ Intl</i>, 76:49-56.</p> <p><b>Question 5:</b> I am not the best to answer this question.</p> <p><b>Question 6:</b> Yes, given the prevalence of brominated analogues, I support the current recommendations to use TEFs for calculating TEQs so that these compounds are included. As new data comes available, the use of TEFs should be re-evaluated.</p> <p><b>Question 7:</b> No.</p> |
| <p><b>Dr. Qiaoxiang (Daisy) Dong</b></p> <p>11-28-2023</p> | <p><b>Question 1:</b> Yes, van den Berg et al. 2013 proposed to use the TEF values of chlorinated congeners for their brominated analogues. Although the paper stated that these are interim TEF values and there are limited studies for PBDDs/PBDFs when compared with</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|  | <p>PCDDs/PCDFs, the paper provides strong scientific evidence to use similar TEF values for brominated congeners.</p> <p><b>Question 2:</b> Yes.</p> <p><b>Question 3:</b> Yes, the evidence is strong based on available literature at the time the paper was published.</p> <p><b>Question 4:</b> An earlier study by Shaw et al. 2013 used TEFs of PCDD/Fs to calculate the risk of PBDD/Fs for firefighters. More recently, Budin et al., 2020 used this approach to assess the risk of PBDD/Fs contained in plastic toys for children. See below for the references and I also attached the PDF files of these two papers in the email.</p> <p>Susan D. Shaw, Michelle L. Berger, Jennifer H. Harris, Se Hun Yun, Qian Wu, Chunyang Liao, Arlene Blum, Anthony Stefani, Kurunthachalam Kannan, Persistent organic pollutants including polychlorinated and polybrominated dibenzo-p-dioxins and dibenzofurans in firefighters from Northern California, Chemosphere, Volume 91, Issue 10, 2013, Pages 1386-1394, ISSN 0045-6535,<br/> <a href="https://doi.org/10.1016/j.chemosphere.2012.12.070">https://doi.org/10.1016/j.chemosphere.2012.12.070</a>.</p> <p>Clémence Budin, Jindrich Petrlik, Jitka Strakova, Stephan Hamm, Bjorn Beeler, Peter Behnisch, Harrie Besselink, Bart van der Burg, Abraham Brouwer, Detection of high PBDD/Fs levels and dioxin-like activity in toys using a combination of GC-HRMS, rat-based and human-based DR CALUX® reporter gene assays, Chemosphere, Volume 251, 2020, 126579, ISSN 0045-6535,<br/> <a href="https://doi.org/10.1016/j.chemosphere.2020.126579">https://doi.org/10.1016/j.chemosphere.2020.126579</a>.</p> <p><b>Question 5:</b> I am not aware of any government agencies implementing this proposal.</p> <p><b>Question 6:</b> Yes, I would recommend applying existing TEFs to brominated analogues.</p> <p><b>Question 7:</b> Unless there are disagreements among ATSAC members, there is no need to have a virtual meeting.</p> |
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## Contact

Cleaner Air Oregon, [cleanerair@deq.oregon.gov](mailto:cleanerair@deq.oregon.gov)

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# 1-Methylnaphthalene ATSAC Feedback Organizer

The purpose of this document is to compile ATSAC member feedback during DEQ's [TAC Review and Update Rulemaking](#).

## Background

DEQ and OHA requested written responses from ATSAC members in response to a nationwide state risk assessor group email, received September 3, 2024, about the 2024 PPRTV 1-methylnaphthalene noncancer chronic reference concentration (RfC; see email below forwarded to ATSAC February 20, 2025). The 2024 PPRTV documentation for 1-methylnaphthalene can be found [online here](#). In the ATSAC TRV review materials, 1-methylnaphthalene information is in ATSAC Workbook #2 on the [ATSAC website](#) (see row #416 on appendix tab #6). ATSAC members were asked to review the PPRTV documentation for 1-methylnaphthalene and answer the following question: **Do you support or have concerns about the 1-methylnaphthalene PPRTV noncancer chronic RfC?**

**ATSAC members' written responses were submitted to OHA in March 2025 and compiled into this document.**

## Email from Nationwide Listserv Forwarded to ATSAC (February 20, 2025)

*"The May RSL update included a PPRTV Reference Concentration (RfC) for 1-Methylnaphthalene (3E-06 mg/m3). At first, I just noted the change and updated our table of VISLs and RSL accordingly. However, as we have been addressing sites with 1-Methylnaphthalene (1-MN) we have noticed that it is suddenly a primary risk driver at many sites. Thus, I did some digging and wanted to see if any of my colleagues in other states have similar concerns about this PPRTV RfC.*

*The paper used to create the RfC is from a subchronic study that did not follow an established protocol (at least not completely), that had an Uncertainty Factor of 3000 and yielded a "low confidence" rating from PPRTV. Importantly, it was unclear if the response to nasopharyngeal tissues were adverse (toxic) or adaptive (reversible).*

*Furthermore, the other toxicity values for 1-MN (CSF & RfD) are very similar (within one order of magnitude) to the other two Naphthalenes (2-MN and Naph), and almost all of the chemical-specific parameters (HLC, VP, Solubility, Koc, etc.) are very similar (on the same order of magnitude). Thus, this RfC for 1-MN appears to be a significant departure from what was previously understood about the Naphthalenes in general, indicating either it is suspect or all of the other toxicity values are suspect, or both.*

*The programmatic implications of this new RfC value are considerable. 1-MN will now drive many of the risks at gasoline and diesel release sites much more than Benzene or Naphthalene. The Tapwater RSL is 0.0063 ug/L, which likely cannot even be detected. In fact, EPA updated the Industrial Groundwater VISL to 1.6 ug/L (based on HI=1.0) compared to a Benzene Industrial VISL of 118 ug/L (based on ELCR=1E-06). Meanwhile LUST sites rarely even sample for 1-MN or 2-MN and completely ignore their risks.*

*EPA Region 3 is planning on using this new RfC value, but I am having sincere doubts about the validity of this new RfC. Private-sector Toxicologists have contacted me to complain about this RfC (one asking us to reject it) and I was wondering if other states were having the same concerns or issues, and if so, how are you addressing them? Some options I have thought of:*

- 1. Accept it and move on with significant alterations to our programs*
- 2. Reject it and keep the status quo*
- 3. Reject it and use route-to-route extrapolation to develop a RfC (0.28 mg/m<sup>3</sup>)*
- 4. Reject it and use the Naphthalene RfC as a surrogate (I do not think 1-MN is appropriate for route-to-route extrapolation), which strikes a compromise by accounting for non-cancer inhalation risks but using a value with much higher confidence (albeit for a slightly different chemical)."*

# ATSAC Member Written Responses

## John Budroe, PhD

*The Oregon Department of Environmental Quality (DEQ) has proposed to establish a chronic Toxicity Reference Value (TRV) for 1-methylnaphthalene (1-MN) of  $0.003 \mu\text{g}/\text{m}^3$ . This TRV is directly adopted from the chronic provisional Reference Concentration (p-RfC) of  $0.003 \mu\text{g}/\text{m}^3$  developed by the US EPA Provisional Peer-Reviewed Toxicity Value (PPRTV) program (US EPA, 2024).*

*The p-RfC is based on a 13-week inhalation study using 10 male and 10 female F344 rats, exposed 6 hours/day, 5 days/week (Kim et al., 2020). Nominal exposure concentrations were 0, 0.5, 4 and 30 ppm. US EPA identified increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in males and females and increased incidence of transitional epithelial cell hyperplasia in nasopharyngeal tissues in males as the critical study effects.*

*The study effects data were modeled using the dichotomous models contained in US EPA's Benchmark Dose Software (BMDS, version 3.2). The dose metric employed was the Human Equivalent Concentration (HEC) based on extrathoracic effects ( $\text{HEC}_{\text{ET}}$ ), and a benchmark response (BMR) of 10% extra risk for incidence data was used. The  $\text{HEC}_{\text{ET}}$  was calculated using study-specific time-weighted average body weights for each exposure group. US EPA chose the 10% benchmark concentration lower confidence limit ( $\text{BMCL}_{10}$ ) on the  $\text{HEC}_{\text{ET}}$  of  $0.009 \text{ mg}/\text{m}^3$  ( $0.0015 \text{ ppm}$ ,  $1 \text{ ppm} = 5.91 \text{ mg}/\text{m}^3$ ) for increased incidence of mucous cell hyperplasia in nasopharyngeal tissues in male F344 rats as the lowest point-of-departure (POD) for derivation of both a subchronic and chronic 1-MN p-RfC. The best fitting model for this endpoint was the multistage 1-degree.*

*The subchronic 1-MN p-RfC was derived by dividing the POD of  $0.009 \text{ mg}/\text{m}^3$  by a composite uncertainty factor ( $\text{UF}_c$ ) of 300 ( $\text{UF}_A = 3$  (animal-human extrapolation, including HEC derivation)  $\times \text{UF}_D = 10$  (database uncertainty)  $\times \text{UF}_H = 10$  (interhuman variability)  $\times \text{UF}_L = 1$  (POD is a  $\text{BMCL}$ )  $\times \text{UF}_S = 1$  (subchronic data used)), resulting in a value of  $3 \times 10^{-5} \text{ mg}/\text{m}^3$  ( $0.03 \mu\text{g}/\text{m}^3$ ,  $5 \times 10^{-4} \text{ ppb}$ ).*

*US EPA also developed a chronic 1-MN p-RfC from the same data set and methodology used to develop the subchronic 1-MN p-RfC, with the exception that a  $\text{UF}_S$  of 10 was used to account for subchronic to chronic extrapolation, resulting in a  $\text{UF}_c$  of 3000, and a chronic 1-MN p-RfC of  $3 \times 10^{-6} \text{ mg}/\text{m}^3$  ( $0.003 \mu\text{g}/\text{m}^3$ ;  $5 \times 10^{-5} \text{ ppb}$ ).*

*The Agency for Toxic Substances and Disease Registry (ATSDR) released a Toxicological Profile (TP) for Naphthalene, 1-Methylnaphthalene and 2-Methylnaphthalene (Draft for Public Comment) in May 2024 (ATSDR, 2024). This document used the same data set and adverse effect endpoints (Kim et al., 2020) to develop an intermediate (15 – 364 days exposure) Minimal Risk Level (MRL) that US EPA used to develop subchronic and chronic 1-MN p-RfC values. The study effects data were modeled using BMDS version 3.2. The dose metric employed was exposure concentration.*

*ATSDR chose the  $\text{BMCL}_{10}$  for increased incidence of mucous cell hyperplasia in male F344 rat nasopharyngeal tissues generated using a dichotomous Hill model as the lowest appropriate POD for deriving an intermediate 1-MN MRL. The  $\text{BMCL}_{10}$  was adjusted for exposure duration and converted to a  $\text{BMCL}_{10\text{HEC}}$  of  $0.0027 \text{ ppm}$  ( $0.016 \text{ mg}/\text{m}^3$ ). The  $\text{BMCL}_{10\text{HEC}}$  was then divided by a composite uncertainty factor ( $\text{UF}_c$ ) of 30 ( $\text{UF}_A = 3$  (animal-human extrapolation, including HEC derivation)  $\times \text{UF}_H = 10$  (interhuman variability)), resulting in an intermediate 1-MN MRL of  $0.00009 \text{ ppm}$  ( $0.09 \text{ ppb}$ ;  $0.05 \mu\text{g}/\text{m}^3$ ).*

*There are some small methodological differences between the 1-MN intermediate MRL and subchronic/chronic p-RfC derivations. For the HEC calculations, ATSDR appeared to use default physiological parameters for the study animals, as compared to US EPA's use of study-specific time-weighted average body weights for each exposure group to develop an HEC. Additionally, ATSDR used a dichotomous Hill model to generate a POD for*



male F344 rat 1-MN-induced nasopharyngeal tissue mucous cell hyperplasia, while US EPA used a multistage 1-degree model for the same purpose. However, the PODs differ by less than 2-fold (US EPA 0.009 mg/m<sup>3</sup>; ATSDR 0.016 mg/m<sup>3</sup>).

Also, ATSDR deciding not to use the Kim et al. (2020) 13-week exposure data to develop a chronic MRL is a policy choice. Both US EPA IRIS and the California Office of Environmental Health Hazard Assessment (OEHHA)(two of DEQ's authoritative sources) will develop RfCs and chronic RELs, respectively, from subchronic exposure data. Having both US EPA and ATSDR decide that the Kim et al. data (2020) are useful for developing subchronic health values and the similarity of the PODs that were calculated indicate that the use of the 1-MP chronic p-RfC to develop a chronic TRV is appropriate.

However, DEQ may wish to consider revising some of the UFs that US EPA used to generate the 1-MN chronic p-RfC from the POD. For example, US EPA used a UF<sub>D</sub> of 10 (database uncertainty) and a UF<sub>S</sub> of 10 (subchronic to chronic extrapolation). In this case, OEHHA would use a UF<sub>D</sub> of 3 and a UF<sub>S</sub> of 3 (OEHHA considers 13-week studies to be subchronic). This would reduce the UF<sub>C</sub> to 300, and result in a 1-MN chronic TRV of 0.03 µg/m<sup>3</sup>.

## References

Kim YS, Lee MJ, Seo DS, et al. 2020. Thirteen-week inhalation toxicity study of 1-methylnaphthalene in F344 rats. *Toxicol Res* 36(1):13-20.

U.S. Environmental Protection Agency (US EPA). Provisional Peer-Reviewed Toxicity Values for 1-Methylnaphthalene (CASRN 90-12-0). Center for Public Health and Environmental Assessment, Office of Research and Development Cincinnati, OH 45268. EPA/690/R-24/001F. March 2024.

Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Naphthalene, 1-Methylnaphthalene and 2-Methylnaphthalene. Draft for Public Comment. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. May 2024.

## Daisy Dong, PhD

I took a detailed look at the PPRTV document. I have to say it is too shady for them to run benchmark dose modeling on the histopathological data of the nasopharyngeal tissues. I also dig into the critical study (Kim et al, 2020) they used for POD derivation. I have to say that I agree with authors' conclusion that the NOAEL should be 4 ppm because 1) the HE readings are mostly minimal or mild in 4 ppm group; 2) most likely these are adaptive responses, and 3) negative findings in 4 ppm for all other parameters measured. This POD (NOAEL=4 ppm) is more solid than the BMCL10 from the PPRTV document. I did some calculations based on the NOAEL = 4 ppm and the derived chronic TRV would be 0.83 or 4.14 µg/m<sup>3</sup> depending on which RGDR default value to pick (see attached files).

Thus, I don't advise adopting the PPRTV chronic RfC. Rather, I think ATSAC members can help DEQ calculate a new TRV based on the PPRTV document.

## Chronic TRV for 1-methylnaphthalene based on Kim 2020 study

Based on study author, **NOALE =4 ppm** (I agree with the study author given the overall assessments of all parameters and the minimal and mild effects noted in the histopathological finding of the nasopharyngeal tissues.

Exposure: F344 rat, 6 hours/d, 5 days/wk, 13 weeks total (a subchronic inhalation study-whole body)

| Parameters                                                                       | Method 1                            | Method 2                         |
|----------------------------------------------------------------------------------|-------------------------------------|----------------------------------|
| POD =NOAEL=4 ppm x 5.8*= 23.2 mg/m <sup>3</sup>                                  | 23.2                                | 23.2                             |
| POD <sub>ADJ</sub> = POD x (6/24) x (5/7), mg/m <sup>3</sup>                     | 4.14                                | 4.14                             |
| DAF (either use EPA 1994 or EPA 2012 default value for extrathoracic region, ET) | RGDR <sub>ET</sub> =0.20 (EPA 1994) | RGDR <sub>ET</sub> =1 (EPA 2012) |
| POD <sub>HEC</sub> = POD <sub>ADJ</sub> X DAF, mg/m <sup>3</sup>                 | 0.83                                | 4.14                             |
| UF <sub>A</sub>                                                                  | 3                                   | 3                                |
| UF <sub>H</sub>                                                                  | 10                                  | 10                               |
| UF <sub>DB</sub>                                                                 | 10                                  | 10                               |
| UF <sub>SUB</sub>                                                                | 3                                   | 3                                |
| UF <sub>TOTAL</sub>                                                              | 1000                                | 1000                             |
| TRV= POE <sub>HEC</sub> /UF <sub>TOTAL</sub> X 1000, µg/m <sup>3</sup>           | <b>0.83</b>                         | <b>4.14</b>                      |

\*The conversion factor for 1-methylnaphthalene is 1 ppm=5.8 mg/m<sup>3</sup> (Formula=MW/24.45, MW=142.20 g/mol)

## John Stanek, PhD

*John Stanek recused himself from the email thread because he worked on the PPRTV chronic RfC in some capacity recently as part of his role at EPA.*

## Susan Tilton, PhD

*The request for the committee is to consider the proposed TRV for chronic 1-MN adopted from the EPA PPRTV of 0.003 ug/m3 and the questions proposed by WVDEP about the relevance of the underlying study used to derive the POD (Kim et al 2020). Based on the prevalence of 1-MN in studies collected by our program, it is understandable that 1-MN could potentially drive risk due to abundance when measured. I agree with using the Kim et al study as the basis for deriving the POD for the EPA PPRTV. Mucous cell hyperplasia in the nasopharyngeal tissue was used as the critical effect and even though the authors recommended a NOAEL of 4ppm, effects were observed in tissues at this dose that were relevant to the critical effect in a 13-week inhalation study with male and female F344 rats based on dose and severity. Therefore, I would support the EPA's use of the data from Kim et al (2020) for determining a POD rather than using a NOAEL of 4ppm as recommended in Kim et al (2020). This would be consistent with (1) prior reports for evidence of respiratory irritation from 1-MN (Korsak et al 1998), (2) the recommendation by the American Conference on the Governmental Industrial Hygienists for a lower acute threshold limit value of 0.5ppm, (3) the observation in a prior study with 1-MN that adverse effects (pulmonary alveolar proteinosis in the lung) were related to duration of exposure and only observed after chronic exposure (Murata et al 1992), and (4) the expectation by the authors (Kim et al.) that chronic exposure to 1-MN by inhalation exposure may cause lesions in the lung based on the observed tissue effects.*

*I am not able to comment on the BMD approach used to calculating the BMDL10 (HECet) and so other's may be able to provide input here, but it was based on the BMDL10 for the most sensitive endpoint for deriving a subchronic and chronic provisional reference concentration. Based on default UFs reported by OEHHA, which have previously been adopted by Oregon DEQ for other TRVs, I support John's recommendation of reducing uncertainty for UFd and UFsub (based on the 13-week study) to 3 for consistency.*

Kim YS, Lee MJ, Seo DS, et al. 2020. Thirteen-week inhalation toxicity study of 1-methylnaphthalene in F344 rats. Toxicol Res 36(1):13-20.

Murata Y, Denda A, Maruyama H, Konishi Y (1992) Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice. Toxicol Sci 21:44–51.

American Conference of Governmental Hygienists Inc. (2017) 1-Methylnaphthalene and 2-methylnaphthalene. Documentation of the threshold limit values and biological exposure indices, 7<sup>th</sup> edn.

Korsak Z, Majcherek W, Rydzynski K (1998) Toxic effects of acute inhalation exposure to 1-methylnaphthalene and 2-methylnaphthalene in experimental animals. Int J Occup Med Environ Health 11:335–342.

## **John Vandenberg, PhD**

*I reviewed the PPRTV document and the comments from Daisy and John Budroe were very useful.*

*I also considered the cancer and oral data provided in the PPRTV document to get a sense of the other studies available for this chemical. I found the cancer and oral study data to indicate effects of concern were observed from other study designs and via the oral route of exposure.*

*This is a case where the ATSAC may be helpful, but it is clear that within the group we may have different opinions as to the path forward.*

*In my opinion the data are suitable for benchmark dose modeling as done by EPA (and also ATSDR in their draft report). The key question then is the application of uncertainty factors to the BMCL10hec to derive a chronic Reference Concentration.*

*My preferred approach would be to follow the PPRTV application of uncertainty factors, i.e. apply 3-fold UF<sub>a</sub> for animal-human extrapolation, 10-fold UF<sub>h</sub> for human variability and susceptibility, and 10-fold UFs for subchronic to chronic extrapolation, a 1-fold UF<sub>i</sub> for use of BMCL as POD, and 10-fold UF<sub>d</sub> for database uncertainty, resulting in a total UF of 3000 (as described on page 39 of the PPRTV document). With PPRTV documents considered as an "authoritative source" I support the use of the EPA PPRTV evaluation for 1-methylnaphthalene.*

## **Contact:**

Oregon Department of Environmental Quality  
Cleaner Air Oregon Program  
[cleanerair@deq.oregon.gov](mailto:cleanerair@deq.oregon.gov)

## **Prepared By:**

This document was prepared by Oregon Health Authority. Authors:

Holly Dixon, PhD  
Public Health Toxicologist

David Farrer, MS, PhD  
Public Health Toxicologist

Dana Crosby, MPH  
Environmental Health Assessment Program Coordinator



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# Perfluorodecanoic acid (PFDA) ATSAC Feedback Organizer

## Background

In June 2025, DEQ and OHA requested written responses from members of the Air Toxics Science Advisory Committee (ATSAC) in response to a question regarding the proposed TRV for perfluorodecanoic acid (PFDA). The purpose of this document is to compile ATSAC member feedback during DEQ's [TAC Review and Update Rulemaking](#).

## DEQ and OHA Email to ATSAC

*"We did run across one more question about one of our proposed TRVs where "DEQ in consultation with ATSAC" is the authoritative source. The currently proposed chronic noncancer TRV for perfluorodecanoic acid (PFDA) (CASRN 335-76-2) comes from the [Texas Commission on Environmental Quality \(TCEQ\)](#) unmodified and is 0.053 µg/m<sup>3</sup> (see last table of "[Document 4: TRVs Where DEQ is the Authoritative Source](#)" page 32. TCEQ derived this value by a simple route to route extrapolation from their own 2023 oral reference dose for the same compound. They employed the simple route to route formula:*

$$\text{Oral RfD in } \frac{\text{mg}}{\text{kg} \cdot \text{day}} \times \frac{70 \text{ kg body weight}}{20 \text{ m}^3/\text{day}} = \text{RfC in mg/m}^3$$

*DEQ and OHA would like to apply the same route to route extrapolation equation to the more recent, 2024 IRIS oral RfD for PFDA instead of the TCEQ oral RfD that the agencies proposed to you in previous meetings. This change would bring our TRV closer to our Authoritative Sources listed in rule. The final value would be:*

$$2 \times 10^{-9} \frac{\text{mg}}{\text{kg} \cdot \text{day}} \times \frac{70 \text{ kg body weight}}{20 \text{ m}^3/\text{day}} = 7 \times 10^{-9} \frac{\text{mg}}{\text{m}^3} = 7 \times 10^{-6} \frac{\mu\text{g}}{\text{m}^3}$$

*Do you agree with or have concerns about this proposed update?"*

**ATSAC members' written responses were submitted to OHA in June 2025 and compiled into this document.**

# ATSAC Member Written Responses

## John Budroe, PhD

*A tabular summary of the information used by US EPA IRIS (2024) and TCEQ (2023) to develop RfDs for perfluorodecanoic acid (PFDA) is listed below:*

| Agency                        | TCEQ                           | US EPA IRIS                                                                           |
|-------------------------------|--------------------------------|---------------------------------------------------------------------------------------|
| Critical studies              | Kawashima et al. (1995)        | Grandjean et al. (2012), Budtz-Jørgensen and Grandjean (2018), Wikström et al. (2020) |
| Sex, species                  | male rats                      | male, female human children                                                           |
| Exposure duration             | subacute                       | chronic                                                                               |
| Endpoint                      | increased liver weight         | decreased immune system response, decreased body weight                               |
| Cumulative uncertainty factor | 81000                          | 30                                                                                    |
| RfD                           | $1.5 \times 10^{-5}$ mg/kg-day | $2 \times 10^{-9}$ mg/kg-day                                                          |

*The information above indicates:*

- 1) IRIS used newer studies than TCEQ to develop a PFDA RfD. Although these studies were available to TCEQ, they were not discussed in the 2023 document.*
- 2) IRIS used human data to develop a PFDA RfD; TCEQ used animal data for the same purpose. The use of human data instead of animal data for chemical risk assessment where possible is generally preferred.*
- 3) The exposure duration of the critical studies used to develop the IRIS RfD (chronic) were more appropriate compared to the exposure duration of the study used to develop the TCEQ PFDA RfD (subacute).*
- 4) The IRIS PFDA RfD was developed using an endpoint (decreased immune system response) observed in a sensitive subpopulation (children).*
- 5) The TCEQ PFDA RfD cumulative uncertainty factor is far greater than 3000 (the maximum used by OEHHHA and IRIS), and is over three orders of magnitude greater than the IRIS PFDA RfD cumulative uncertainty factor.*
- 6) The IRIS PFDA RfD is substantially more health protective than the TCEQ PFDA RfD.*

*On the basis of this information, I agree with the proposal by OHA and DEQ to change from using the TCEQ PFDA RfD to the IRIS PFDA RfD as the basis for developing a PFDA TRV via route-to-route extrapolation.*

## Daisy Dong, PhD

*I agree with the use of 2024 IRIS oral RfD to do route-to-route extrapolation for PFDA TRV.*

## John Stanek, PhD

*I agree with the use of the updated IRIS value for calculating a TRV for PFDA.*

## Susan Tilton, PhD

*I don't have any concerns with the use of the IRIS PFDA RfD for route-to-route extrapolation.*

## John Vandenberg, PhD

*I reviewed the IRIS (2024) and TCEQ (2023) documents on PFDA and summaries of critical studies.*

*From my review I see that although the TCEQ document is dated 2023 it does not appear that several critical studies cited by IRIS (2024) were considered.*

*The newer studies include recent results in ~1500 infants (Wikstrom et al, 2020 - abstract attached below) plus studies showing effects in children (Grandjean et al. (2012); BudtzJørgensen and Grandjean, 2018) and the resulting RfD based on effects in infants and children is much lower than that derived by TCEQ.*

*Based on the consideration of more recently published studies I conclude that the IRIS (2024) document should be used as the authoritative source for TRV derivation.*

*Please note that the Wikstrom et al study included similar results for several PFAS that may affect other TRVs.*

*I agree with the proposal by OHA and DEQ to use route-to-route extrapolation to derive an RfC from the IRIS (2024) RfD for PFDA.*

### Title

Maternal serum levels of perfluoroalkyl substances in early pregnancy and offspring birth weight

### Author(s)

Wikström, S; Lin, PI; Lindh, CH; Shu, H; Bornehag, CG

### Year

2020

### DOI

[10.1038/s41390-019-0720-1](https://doi.org/10.1038/s41390-019-0720-1)

### Abstract

**BACKGROUND:** Perfluoroalkyl substances (PFASs) are widespread, bioaccumulating, and persistent and show placental transfer. Emerging research indicates associations between prenatal exposure and low birth weight. The aim of this study was to assess the associations between first trimester exposure to PFASs and birth weight (BW) in the Swedish Environmental, Longitudinal, Mother and child, Asthma and allergy (SELMA) study and examine whether associations differ between girls and boys.

**METHODS:** Eight PFASs were analyzed in maternal serum (median: 10 weeks of pregnancy). Associations between prenatal PFAS exposure and birth outcomes with BW, BW for gestational age, and birth small for gestational age (SGA) were assessed in 1533 infants, adjusted for potential confounders and stratified by sex.

**RESULTS:** Increased maternal perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) were associated with lower BW, lower BW for gestational age, and SGA birth. Associations were significant only in girls, where prenatal exposure in the upper quartile was associated with a 93-142-g lower BW when compared with that of the lowest quartile exposure. The associations were not mediated by effects on gestational age.

**CONCLUSIONS:** We found associations between prenatal exposure for five different PFASs and birth weight, with more pronounced associations in girls than in boys.

## Contact:

Oregon Department of Environmental Quality  
Cleaner Air Oregon Program  
[cleanerair@deq.oregon.gov](mailto:cleanerair@deq.oregon.gov)

## Prepared By:

This document was prepared by Oregon Health Authority. Authors:

Holly Dixon, PhD  
Public Health Toxicologist

David Farrer, MS, PhD  
Public Health Toxicologist

Dana Crosby, MPH  
Environmental Health Assessment Program Coordinator



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**Appendix S: Adoption of 2022 World  
Health Organization Toxic Equivalency  
Factors (TEFs) for Polychlorinated  
Dioxins, Dibenzofurans, and  
Biphenyls: OHA Deputy State  
Epidemiologist Memorandum**

# Memorandum

**To:** Cleaner Air Oregon OHA Toxicology Team; David Farrer, Public Health Toxicologist; Holly Dixon, Public Health Toxicologist

**From:** Ali Hamade, PhD DABT, Deputy State Epidemiologist

**Date:** September 25, 2025

**Subject:** Opinion on adoption of the 2022 World Health Organization mammalian toxic equivalency factors for polychlorinated dioxins, dibenzofurans, and biphenyls for risk evaluation purposes

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In 2005, the [World Health Organization](#) (WHO) convened a panel of international experts that reevaluated the dioxins and dioxin-like compounds toxic equivalency factors (TEFs) first developed in 1998 (1, 2). In developing TEFs, the 2005 panel relied on expert judgement and consensus-based TEFs. However, the panel identified a need for a quantitative approach for dose response assessment and a probabilistic approach to develop TEFs that better describes the uncertainty around the TEFs.

In 2022, with these recommendations in mind, the WHO convened another panel of experts that reevaluated the TEFs with 1) an updated relative effect potencies (REP) database (from which TEFs are derived), 2) a consensus-based REP weighting process, and 3) a Bayesian dose response modeling and meta-analysis to derive “Best-Estimate” TEFs” (3). The following is an overview of the components of this process.

## *Relative Effect Potencies Database*

The updated database included 1,269 REP values as compared to 634 REP values in the earlier database in 2004, in addition to many more studies published through 2021 (4). Included studies had to 1) be peer-reviewed and have dose-response data for the reference compound and at least one dioxin-

like compound, 2) have statistically significant responses compared to untreated or vehicle control, and 3) include non-marine mammals, a mammalian cell line, or cells transfected with a relevant sequence. The database was reviewed by a contractor that found it met WHO criteria, an aspect which increases confidence in the database. Previous database versions were not similarly reviewed (3).

#### *Consensus-based weighting framework to assess REP quality and relevance*

The 2022 panel used a consensus-based approach to identify six study characteristics (study type, study model, pharmacokinetics, REP derivation method, REP derivation quality, endpoint) as most important for weighting REP quality as relevant to human risk. Studies were accordingly assigned quality category scores, but categorizations were not used as weighting scores per se; rather, they were used to train a machine learning model to quantitatively integrate the weighting parameters in a Bayesian-inference model (and reproduce the expert panel judgement) (3, 5). The 2022 panel identified study type, REP derivation method, and pharmacokinetics similarity as contributing most to the quality categorizations. The 2005 WHO expert panel had prioritized data based on study type, duration, and endpoint.

#### *Quantitative integration of weighting framework via Bayesian-inference meta-analysis*

Bayesian meta-analysis was performed by combining all data for a congener including dose-response modeling, standardization, and machine learning quality weighing. This resulted in a single dose-response fitted to the data by deriving congener-specific standardized Hill model parameters for congeners and reference compounds. This meta-analysis provided a “Best-Estimate TEF” with associated uncertainty distribution. The model’s prediction is influenced more by datasets of a higher weight (3).

In summary, the 2022 WHO panel used a multistep method that combines Bayesian dose-response fit and meta-analysis with a machine learning model of REP quality categorizations to predict the most likely relationship between congeners and reference compound with associated TEF uncertainty distributions.

As Ring et al. (2023) (6), the authors who developed the Bayesian model concept for this work, and some of whom served on the WHO panel, stated “*This method represents a vast improvement over the currently used qualitative approach [2005 panel], which derives a point-estimate TEF and does not quantify uncertainty. The ultimate result of this method development is an objective, automated, and quantitative workflow that can derive TEFs from all available evidence without requiring expert judgement.*”

Noteworthy, in presenting the 2022 re-evaluation of the TEFs, Devito et al. (2024) (3) indicated that the derived point-estimate TEFs are best for use in risk assessment. While the uncertainty around these estimates is an important improvement for this round of TEF derivation, Devito et. al. (2024) states they are unreliable for risk management purposes. This is because the uncertainty ranges around the TEFs are based on mathematical plausibility rather than toxicological plausibility and the model did not incorporate potential correlations among REPs for endpoints or congeners measured by the same lab (3).

The evaluation and reevaluation efforts included an impressive gathering of academic, government, and private scientists in the fields of toxicology, risk assessment, and public health including from the United States (US Environmental Protection Agency and National Institutes of Health). The WHO is the leading authority on international health at the United Nations that has led the development of guidelines and assessments of air pollution health effects, chemical risks in food, communicable diseases, food safety, and many other topics of environmental and public health importance. Countries and agencies can adopt WHO opinions and guidelines. The Agency for Toxic Substances and Disease Registry, one of DEQ’s Authoritative Sources listed in Oregon Administrative Rule (OAR 340-247-0030), has adopted the 2022 WHO TEFs (7).

Given all the above, this reviewer finds the most recent WHO derivation of TEFs (2022) to be more advanced than previous versions due to inclusion of more data and quantitative and probabilistic methods. The 2022 WHO TEFs may be used for chemical risk evaluation in the context of Oregon Department of Environmental Quality’s inhalation toxicity reference values.

## References

1. Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicol Sci.* 2006 Oct;93(2):223-41. doi: 10.1093/toxsci/kfl055. Epub 2006 Jul 7. PMID: 16829543; PMCID: PMC2290740.
2. Van den Berg M, Birnbaum L, Bosveld AT, Brunström B, Cook P, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, Kubiak T, Larsen JC, van Leeuwen FX, Liem AK, Nolt C, Peterson RE, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Waern F, Zacharewski T. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ Health Perspect.* 1998 Dec;106(12):775-92. doi: 10.1289/ehp.98106775. PMID: 9831538; PMCID: PMC1533232.
3. DeVito M, Bokkers B, van Duursen MBM, van Ede K, Feeley M, Antunes Fernandes Gáspár E, Haws L, Kennedy S, Peterson RE, Hoogenboom R, Nohara K, Petersen K, Rider C, Rose M, Safe S, Schrenk D, Wheeler MW, Wikoff DS, Zhao B, van den Berg M. The 2022 world health organization reevaluation of human and mammalian toxic equivalency factors for polychlorinated dioxins, dibenzofurans and biphenyls. *Regul Toxicol Pharmacol.* 2024 Jan;146:105525. doi: 10.1016/j.yrtph.2023.105525. Epub 2023 Nov 14. PMID: 37972849; PMCID: PMC10870838.
4. Fitch S, Blanchette A, Haws LC, Franke K, Ring C, DeVito M, Wheeler M, Walker N, Birnbaum L, Van Ede KI, Antunes Fernandes EC, Wikoff DS. Systematic update to the mammalian relative potency estimate database and development of best estimate toxic equivalency factors for dioxin-like compounds. *Regul Toxicol Pharmacol.* 2024 Feb;147:105571. doi: 10.1016/j.yrtph.2024.105571. Epub 2024 Jan 18. PMID: 38244664; PMCID: PMC11059105.
5. Wikoff D, Ring C, DeVito M, Walker N, Birnbaum L, Haws L. Development and application of a systematic and quantitative weighting framework to evaluate the quality and relevance of relative potency estimates for dioxin-like compounds (DLCs) for human health risk assessment. *Regul Toxicol Pharmacol.* 2023 Dec;145:105500.

doi: 10.1016/j.yrtph.2023.105500. Epub 2023 Oct 21. PMID: 37866700; PMCID: PMC10941990.

6. Ring C, Blanchette A, Klaren WD, Fitch S, Haws L, Wheeler MW, DeVito M, Walker N, Wikoff D. A multi-tiered hierarchical Bayesian approach to derive toxic equivalency factors for dioxin-like compounds. *Regul Toxicol Pharmacol*. 2023 Sep;143:105464. doi: 10.1016/j.yrtph.2023.105464. Epub 2023 Jul 27. PMID: 37516304; PMCID: PMC11110530.

7. [ATSDR] Agency for Toxic Substances and Disease Registry. 2025. Toxic Equivalents Procedure for Dioxin and Dioxin-like Compounds. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. September 3. Available online at: <https://www.atsdr.cdc.gov/pha-guidance/resources/TEQ-for-Dioxin-and-Dioxin-like-Compounds-508.pdf#:~:text=This%20document%20presents%20the%20Agency%20for%20Toxic%20Substances,are%20specially%20handled%20in%20ATSDR%20public%20health%20evaluations>

# **Appendix T: Brief History on Previous Oregon ATSAC for Diesel Particulate Matter Background**

## Appendix T. Brief History on Previous Oregon ATSAC for DPM Background

In 2005 and 2017, previous ATSACs discussed the cancer TRV from OEHHA.

### *Background on Previous ATSACs Compared to the Current ATSAC*

Compared to the current ATSAC, previous versions of ATSAC had a different scope and were comprised of people with expertise in a variety of fields other than toxicology, such as experts in Oregon air emissions monitoring and air dispersion modeling. In practice, the prior ATSAC did considerable TRV review work and presented TRVs as recommendations to DEQ. In 2021, the EQC adopted Oregon Administrative Rule changes that revised the ATSAC rules to: clarify it is a non-decision-making body; sharpen its focus on advising DEQ on updating DEQ TRVs and not developing TRV proposals itself; and require that all ATSAC members have experience relevant to the development and review of toxicity reference values.

### *Previous ATSAC Decision*

In 2005 and 2017, previous ATSACs decided not to recommend the cancer TRV from OEHHA for several reasons including that EPA did not calculate a cancer TRV (even though OEHHA's cancer TRV was available at the time) and that Dr. Garshick, the lead author of the critical study used to derive CalEPA's cancer TRV, publicly argued against CalEPA's value.

ATSAC documentation from 2005 and 2017 also summarizes the available epidemiology studies and acknowledges the scientific uncertainty and significant resource requirements as barriers to Oregon calculating its own cancer TRV for DPM. Overall, prior ATSACs did not develop alternate TRVs. Prior ATSACs decided to recommend the WHO cancer TRV for DPM ( $0.1 \mu\text{g}/\text{m}^3$ ), even though the WHO TRV had already been withdrawn during 2017 ATSAC discussions.

### *Current DEQ Response to Previous ATSAC Recommendations*

DEQ and OHA do not recommend using a cancer TRV that has been withdrawn by the agency that derived it – the World Health Organization value of  $0.1 \mu\text{g}/\text{m}^3$ . DEQ and OHA acknowledge that the cancer DPM TRV from CalEPA has uncertainties. However, having assessed both the critiques of the CalEPA TRV and CalEPA's rationales defending the TRV, DEQ is proposing to use the CalEPA cancer DPM TRV of  $0.0033 \mu\text{g}/\text{m}^3$ .



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