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Memorandum

March 26, 2026

To:	Sharla Moffett, Oregon Business and Industry
From:	Deborah Proctor, ToxStrategies
Subject:	Comments to the OHA TRV Support Document January 2026

This memorandum summarizes ToxStrategies' comments regarding the Oregon Health Authority (OHA) Toxicity Reference Value Support Document. Rules Advisory Committee Version. January 12, 2026, prepared in collaboration with the Oregon Department of Environmental Quality (ODEQ). This memorandum was prepared on behalf of Oregon Business and Industry (OBI).

General Comments

ODEQ and OHA have gone to substantial effort to identify toxicity reference values (TRVs) from a wide collection of guidance values. The important distinction that should be carefully considered is that the toxicity criteria being applied, or modified and then applied, as TRVs are guidance. In other states and for federal enforcement, these data are used by risk managers to inform risk management decisions. However, that is not the case under Cleaner Air Oregon (CAO) because TRVs are strictly enforced standards. Risk management decisions should be guided by more than broad application of conservative assumptions that, at times, are not applicable to site-specific conditions and will overestimate potential health risks.

For example, is it appropriate to use a TRV based on vanadium pentoxide, when it is understood that the actual vanadium source is not pentoxide, but exists in a form that is known to have lesser toxicity? That is a decision which is typically made by a risk manager, based on site-specific conditions. When OHA and ODEQ finalize a TRV for all forms of vanadium based on the toxicity of vanadium pentoxide, the opportunities to make reasonable and site-specific risk assessment and management decisions are not available because CAO treats TRVs as rules, not guidance, that cannot be modified in the CAO program. Using this as an example, it is recommended that the rule be revised such that sources going through CAO that can show that they emit a form of a metal different than that which is the basis for the toxicity criteria (e.g., emissions of vanadium as an alloy and not as pentoxide) be exempted or allowed to use a more appropriate TRV specific to their emissions.

The current proposed rule introduces hundreds of new TRVs that in some cases are based on data that is of high uncertainty. For example, some TRVs are based on screening Provisional Peer-Reviewed Toxicity Values (PPRTVs)[1], or are modifications of very dated toxicity criteria, and the current and technically-advanced toxicology literature has not been investigated for the chemical. Regardless of how uncertain the TRV may be, the TRV becomes an inflexible rule that may put arbitrary and unrealistic limitations on Oregon industries, while delivering no commensurate or meaningful public health benefit. Further, the legislative intent of using the TRVs as rules may have strayed considerably from using values specifically developed by authoritative sources, to generating hundreds of new values that have been developed in batch-like fashion from many different sources, but without chemical-specific authoritative review of the available science on a chemical-by-chemical basis.

A careful review of a limited number of TRVs identified 11 proposed TRVs (OBI 2025), as described in the comments submitted by OBI, that should be reconsidered using current science. These include some that are based on dated studies and for which newer studies and risk assessment approaches are recommended to substantially improve the scientific underpinnings of the proposed TRV (e.g., phosgene, nickel). In some cases, the conclusions and exclusions that have been determined in the authoritative sources have been disregarded (e.g., California Office of Environmental Health Hazard Assessment (OEHHA)'s exclusion of cobalt in alloy form, and Agency for Toxic Substances and Disease Registry's (ATSDR's) conclusion regarding amorphous silica). It also should be noted that the ATSDR toxicological profile for nickel (2024) has been withdrawn from the ATSDR website pending further review, yet ODEQ continues to use the minimum risk level (MRL) for nickel from the withdrawn toxicological profile in its rulemaking.

These types of concerns are found only after review of both the chemical-specific peer-reviewed literature, and the robust assessments of the authoritative sources. It is challenging to introduce so many new TRVs without a rigorous approach that is similar to that used by the authoritative sources, because the chemical-specific information is critical to informed decision-making. While ATSAC offered comments on the methods used to develop TRVs, ATSAC was not tasked to review the chemical-specific scientific literature or the reports of the authoritative sources.

As such, it is recommended that any TRV developed from a screening PPRTV (Chapter 4) or where ODEQ is designated as the authoritative source (Chapter 5), undergo a rigorous review of the current scientific literature, allowing for comments from the regulatory and scientific communities, similar to the efforts afforded the review of manganese, diesel particulate matter (DPM), and 1-methylnaphtlaene (Chapter 6).

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[1] Screening PPRTVs are only used by EPA for Superfund sites on an as-needed basis, and are sufficiently uncertain that they are 'screening' PPRTVs rather than more generally applied PPRTVs, which have higher confidence. ODEQ has further limited application of screening PPRTVs to values of those with an arbitrary cut off of having no higher than a 3000-fold uncertainty factor.

Specific Chapter Comments

Chapter 2: Background on OHA's Process for Reviewing and Selecting TRVs for Proposal

ODEQ has gone to considerable effort to identify a very large number of proposed TRVs—623 in total, with 237 that were proposed by DEQ in consultation with ATSAC. The proposed TRVs were released in 2025, and the guidance describing how they were developed was only just released in 2026. This reduces the opportunity for public and scientific input on the process, outside of limited consultation with ATSAC, prior to issuing the proposed values.

While the scale of this effort appears to be impressive, the ATSAC is a voluntary group of experts with limited time to rigorously consider the current state of the science for so many TRVs. Public input and input from the scientific community has otherwise been limited. ToxStrategies, a scientific consulting firm retained by Oregon Business and Industry (OBI), prepared comments and suggestions for 11 of the proposed TAC TRVs.[2] Through this process, it became clear that adopting, or modifying and then adopting, values from authoritative sources may not result in the best use of current science or even convey the findings of the extensive reviews performed by the cited authoritative sources (examples to follow).

In particular, for acute values, none of the authoritative sources provide values for 24-hour acute exposures, meaning all such values relied on extrapolations from data selected for an alternative exposure time period. For example, the nickel acute TRV was extrapolated from the ATSDR acute MRL, which was based on a study where rats were exposed 6 hours per day for 5 days per week for 1 and 4 weeks. The definition of acute for ATSDR is up to 14 days. This study fits well with the ATSDR's definition of acute, but not with that used by ODEQ for CAO. Among the papers reviewed by ATSDR for setting the acute MRL, was a paper which provided a no-observed-adverse-effect level (NOAEL) for 24-hour exposures for a sensitive endpoint. ATSDR did not select this paper as the source of its Point of Departure (POD), which is reasonable given ATSDR's definition of acute. However, this study (Buxton et al. 2021) is a high-quality guideline study that is Good Laboratory Practice (GLP) compliant, and it provides an ideal POD for ODEQ's 24-hour TRV because the exposure duration was 24 hours. Thus, by assuming that the authoritative source had adequately reviewed the literature, *albeit* for a different purpose, ODEQ used the ATSDR MRL, when an alternative approach that included a more appropriate POD supports a different value and is presented in the same guidance document (ATSDR 2024). ToxStrategies prepared an abstract for the 2026 Society of Toxicology Conference and presented the alternative 24-hour acute value for nickel (see Attachment A for the poster presentation).

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[2] On October 14, 2025, OBI submitted a letter to ODEQ with comments on the new TRVs for 10 chemicals: a-silica, trivalent chromium, cobalt, fluoride, hydrogen chloride, lead naphthalene, nickel, PFAS compounds, and vanadium. Comments regarding phosgene TRVs have been developed since and are attached.

It is not expected that OHA and ODEQ have the resources to conduct the level of research that was performed to develop an alternative acute value for all TRVs, but allowing the public and scientific community to provide constructive input in a manner that allows for more detailed study of the literature would provide for more informed rulemaking. Thus, it is recommended that the ODEQ provide alternative means for the public, regulated and scientific communities to comment on both the proposed, and current TRVs. The single petition opportunity, which occurred may years ago, predates the current proposal of an additional 623 values. It is recommended that ODEQ and OHA convene the ATSAC to review the comments submitted by OBI, based on the memos prepared by ToxStrategies, and those of other parties interested in the proposed TRVs.

Chapter 3: Groupings of Chemicals (3.4.1 Metal and metalloids)

Metal and metalloids may exist in a very wide variety of physical forms and chemical structures, making it challenging to provide rules that strictly apply to all forms in individual groups. For example, the TRVs for cobalt and cobalt compounds have been subdivided into soluble and insoluble forms, consistent with the OEHHA designations. However, as detailed in comments submitted to ODEQ by OBI (2025), how to define solubility is not specifically described, and OEHHA has exempted certain forms of cobalt from its toxicity values. ODEQ also has not described how to measure solubility in the rulemaking and has not included the exemptions offered by OEHHA in the proposed ODEQ TRVs. As such, the TRVs for cobalt are ambiguous, and the complete opinions of the authoritative source have not been convened within the rulemaking. Given the wide variety of chemical and physical forms of metals and metalloids, it is most appropriate to specify the chemical form used as the basis of the TRV (e.g., cobalt sulfate, vanadium pentoxide, etc.). It is recommended that the rule allow for variance in a Level 4 CAO risk assessment based on scientific evidence specific to inform any alternative TRV that is more consistent with the specific metal or metalloid that is emitted. As a second example, OEHHA has set RELs for soluble forms of trivalent chromium. OEHHA's review of the literature for insoluble trivalent chromium did not result in the determination of RELs for insoluble chromium, only soluble chromium as detailed in comments submitted to ODEQ by OBI. Similarly, the ATSDR's review of acute toxicity data for trivalent chromium resulted in the determination of no acute inhalation MRLs.

However, OHA and ODEQ did not adhere to the findings of these authoritative sources and opted to develop values for insoluble trivalent chromium (different from those developed by OEHHA) and use values that were derived for intermediate exposures (when ATSDR concluded that the acute data were insufficient) regardless of the inconsistency with authoritative sources. This is a considerable deviation from the decisions of the authoritative sources. Further, these agencies are providing guidance values, not rules. The derivation of rules should be specific to the chemical form of the metal or metalloid and not deviate from the decisions of the authoritative source. If the data are insufficient to develop an acute value, as in the case of insoluble trivalent chromium by OEHHA and ATSDR, a value should not be developed by ODEQ.

Section 3.5: Silica

The Development document (OHA 2026) states that "the severity of health effects from inhaled silica depends on the form," which is an extremely important point for silica health guidelines. However, ODEQ's subdivision of all silica into two groups does not adequately differentiate the potential for toxicity of the wide variety of potential effects from the various silica forms. Regarding crystalline silica (c-silica), there are forms of c-silica not specified in the list provided by ODEQ, such as c-silica in bentonite clay and Fuller's Earth, which contains crystalline silica that is mostly occluded with aluminum silicates and does not have reactive surfaces that induce the toxicity associated with other forms of c-silica in this grouping (WHO 2005; Maxim et al. 2016). Omitting this information introduces ambiguity. Are these forms exempt, or will it be interpreted that they should be regulated as c-silica? This should be clarified, and it is recommended that c-silica in bentonite and Fuller's Earth be excluded, as they were in the OSHA silica rule for occupational exposures (OSHA 2016).

As detailed in comments prepared by ToxStrategies and submitted by OBI, in the ATSDR (2019) review of silica, the Agency concluded that the information was insufficient for developing quantitative toxicity values for any period of exposure for any form of amorphous silica (a-silica). Nonetheless, ODEQ selected to disregard the guidance of the authoritative source and use a guidance value developed by Texas Commission on Environmental Quality (TCEQ). If ODEQ continues to propose this value for further consideration, we recommend that ODEQ revise the acute TRV for a-silica to specify that it only applies to fumed amorphous silica rather than the broad toxic air contaminant (TAC) category that is currently listed. Consistent with ATSDR's conclusions, it is not scientifically appropriate to use findings from studies on the fumed silica form of non-crystalline silica and to apply those findings to all silica forms. This example further demonstrates that a robust review of the written guidance from the authoritative source would better inform TRV development.

Chapter 4: Authoritative Source Special Cases

Screening PPRTVs were first developed by the EPA Superfund program in 2008 and are differentiated from PPRTVs by EPA because screening PPRTVs are recognized to have greater uncertainty regarding the underlying data. It is also important to consider that these values are applied in Superfund cleanup programs but not used to assess or regulate air toxics by EPA. Further, a wide range of chemicals may be measured at a Superfund site and thus a toxicity criteria needed for assessment. By comparison, TAC concentrations are estimated based on air dispersion modeling that may rely on conservative emission factors, does not consider environmental degradation, and as a result, due to conservatisms in the model estimates and lack of consideration regarding environmental fate, the levels and existence of a TACs may be inaccurate, and is more uncertain than a measured chemical at a Superfund site.

With these considerations, it is recommended that a reasonable approach is to use screening PPRTV values for screening purposes, but not as rules in CAO. Specifically, it is recommended that screening PPRTVs be considered screening TRVs for CAO, which may

be supplemented with newer or more technically advanced information in a Level 4 risk assessment.

Chapter 5: Proposed TRVs where DEQ is the Authoritative Source

Section 5.2: Acute TRVs calculated from other sources by modifying the exposure time

Acute TRVs that OHA modified by adjusting exposure times from shorter to longer

Although application of time adjustments following Haber's Law may be appropriate for some chemicals, it is recommended that OHA and ODEQ review the scientific literature supporting each chemical for which this correction has been made to ensure it is justifiable based on the current available science. In many cases, the underlying studies of the authoritative sources are dated and not consistent with the state of the science.

For example, it is recommended that ODEQ review comments regarding hydrogen chloride submitted by OBI. Hydrogen chloride (hydrochloric acid) upon inhalation is highly acidic and as such triggers the trigeminal nerve. The 1-hour OEHHA Reference Exposure Level (REL) for hydrogen chloride is based on irritation and was adjusted by dividing the REL by 1/24 hours to correct from shorter to longer exposures. ODEQ applied a 1/24-hour adjust factor despite the comment of one of the ATSAC members, Dr. John Budrow, that application of Haber's Law for sensory irritation is inappropriate. As such, we recommend maintaining the current acute TRV of 2100 $\mu g/m^3$ based on the value published by OEHHA. ODEQ's proposed acute TRV used OEHHA's TRV but added a time adjustment factor of 1/24 hour to calculate the proposed TRV. Federal agencies, such as the National Institute of Occupational Health and Safety (NIOSH) and the National Research Council (NRC), and the scientific literature (Shusterman et al. 2008) which was coauthored by inhalation toxicology experts at OEHHA), support this recommendation.

A second example is the proposed acute TRV for phosgene, as discussed in detail in Attachment B. The acute TRV for phosgene is based on a 1-hour REL published by OEHHA, and divided by 1/24 hours. This REL is quite dated and was last updated by OEHHA in 1999. Since that time, toxicology research related to phosgene has expanded significantly, including a published expert panel report (Pauluhn et al. 2008), multiple new studies in both rats and dogs, and an extensive review to develop a point of departure. Similar to hydrogen chloride, but based on a different mechanism, the acute effects of phosgene do not strictly follow Haber's Law at all concentrations (Pauluhn 2021). It is recommended that the current research for phosgene be reviewed by OHA and ODEQ and in consultation with ATSAC, an alternative value be used as the acute TRV for phosgene.

This type of information cannot be identified using a review of values from authoritative or other sources and requires additional review of the current literature to identify the current and best science to be used to set a TRV. As such, it is recommended that TRVs modified for time adjustments—both shorter to longer and longer to shorter—be reviewed on a chemical-by-chemical basis in consultation with ATSAC. If that recommendation is

overly burdensome, the rule should be modified such that these TRVs be considered screening levels and open to additional and discussion in any Level 4 risk assessments.

Exposure time adjustments from subchronic TRVs to 24-hour acute TRVs

Converting values from shorter to longer time adjustments is likely to be unnecessarily conservative and burdensome to regulated companies in Oregon. It is recommended that similar to other uncertain TRVs, they be treated as screening values, which may be reinvestigated in a Level 4 risk assessment. As an example, the acute TRVs for trivalent and hexavalent chromium are concerning. For hexavalent chromium, the acute 24-hour TRV is based on a study where the median exposure duration is stated to be 2.5 years. Hexavalent chromium is a highly-studied chemical, and the scientific literature likely provides better data for setting an acute 24-hour value, than an occupational epidemiology study where the median exposure is 2.5 years, and the upper-bound likely far longer. This should be revisited either now with this rulemaking, in consultation with ATSAC, or be treated as a screening TRV that may be reinvestigated and revised in a Level 4 risk assessment.

For soluble and insoluble trivalent chromium, the acute noncancer TRVs for soluble and insoluble, and the chronic insoluble TRV are not scientifically supportable, and are not consistent with the approach of the cited authoritative source, ATSDR. OBI has submitted detailed comments regarding these TRVs. Importantly, they are based on a 13-week exposure duration study, and the health effects reported were due, in part and particularly for insoluble chromium, to accumulation of insoluble particulates in lungs of the animals repeatedly exposed for 13 weeks. This is not an effect that could be expected from a 24-hour exposure. Regarding trivalent chromium, due to the limited relevant information, it is recommended that, consistent with the ATSDR and OEHHA sources, 1) ODEQ should not set acute TRVs for soluble and insoluble trivalent chromium, 2) ODEQ should not set a chronic TRV for insoluble trivalent chromium, and 3) chromium in alloy and metalloid forms should be exempted from regulation.

Finally, regarding lead, OBI submitted comments to ODEQ, prepared by ToxStrategies, with a unique application of the EPA All Ages Lead Model (AALM) (EPA 2025) to calculate a 24-hour exposure that maintains blood lead among children, the most sensitive age group, below the target of <1 µg/dl increase in blood lead set by OEHHA. This approach was presented at the 2026 Society of Toxicology Conference, and the presentation is attached in Attachment C. It is recommended that ODEQ and OHA consider this approach, and in consultation with ATSAC and perhaps EPA, to set an acute lead TRV with this methodology.

Review of more current literature

It is not possible to carefully vet all of the values proposed in Table 5-1 given the time constraints and limitations on available resources. It is notable that most of these values are derived from OEHHA (1999), which is 27-year-old guidance, and additionally used research studies that are even older. As an example, phosgene's acute TRV is based on

OEHHA (1999)'s REL that used a study of rats exposed to phosgene for a number of different time periods (60 to 500 minutes) and concentrations (0.1 to 5 ppm) (Dillar et al 1985), and OEHHA selected the NOAEL at 1 hour, which is consistent with its definition of acute. This study is more than 35 years old and the information needed to do a robust dose adjustment factor (DAF) is not presented, although the authors state that it is known that rats are more sensitive than humans. Since Diller et al. (1985) and the OEHHA REL (1999), robust and highly advanced research on phosgene has been conducted, resulting in a new POD (Pauluhun, 2021), with sufficient data to calculate a DAF and human equivalent concentration (HEC) for 24-hour exposures. See Attachment B for a detailed discussion submitted to ODEQ by OBI.

A more rigorous vetting would have readily uncovered additional more recent and refined studies in dogs and rats, all of which were published after the OEHHA REL in 1999. As such, there are more scientifically defensible options to set a more current and robust TRV. The regulated and scientific communities deserve the opportunity to petition or comment to ODEQ to propose more current and scientifically robust values, in consultation with ATSAC.

Chapter 6: Agency Highlighted TRVs

Section 6.2: 1-Methylnaphthatlene

In this section, it's noted that ODEQ assembled the ATSAC to review and comment on the TRV for 1-methylnaphthalene based on the query of a toxicologist in West Virginia. OBI is requesting further review by ODEQ, and consultation by ATSAC, for eleven chemicals. Given that this request is specific to stakeholders in Oregon affected by this rulemaking, it is requested that each chemical for which technical comments were submitted be reviewed at the same level of analysis as that afforded the acute manganese TRV and 1-methylnaphthalene.

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ATTACHMENT A

ToxStrategies Presentation on Alternative Acute Value for Nickel

Acute (24-hour) Nickel Inhalation Reference Concentration for Use in Air Toxics Risk Assessment

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Background

Nickel is a natural element that is released into the atmosphere by natural processes, such as volcanic eruptions, and by anthropogenic sources, such as metal processing and the combustion of fossil fuels. It is estimated that 80% of atmospheric Ni burden is associated with anthropogenic sources (WHO, 2021). Average concentrations of nickel in urban environments are approximately 5 to 30 ng/m^3 (ATSDR, 2024).

Acute inhalation exposure to nickel at high concentrations has been shown to cause a number of adverse health effects, the most sensitive of which are immunotoxicity, respiratory irritation, and tissue damage. Nickel is also a sensitizer and can cause elicitation of dermatitis and asthma among sensitized individuals.

Several state air toxics control programs, including those in Minnesota, Texas and Oregon, assess potential hazards for peak 24-hour exposures to protect against acute effects. However, federal sources for acute standards use differing definitions of acute exposure. For example, the Agency for Toxic Substances and Disease Registry (ATSDR) acute inhalation Minimum Risk Level (MRL) uses an exposure period of 1 to 14 days, and the US Environmental Protection Agency (EPA) and National Research Council Acute Guideline Exposure Levels (AEGLs) are for exposures up to 8 hours in duration (**Table 1**). As a result, state agencies have taken a variety of approaches to develop acute values for specific exposure durations, including adopting federal values regardless of the lack of a common definition of 'acute,' adjusting the exposure durations to meet the needs of their programs, and/or developing state-specific values, resulting in considerable inconsistency.

While Oregon has proposed using the acute ATSDR MRL as its 24-hour acute Threshold Limit Value (TLV) (ODEQ, 2026), ATSDR has since withdrawn the 2024 Nickel Toxicological Profile and MRLs pending further review.

Table 1. Acute Ni inhalation toxicity criteria

Nickel Form	Agency	Exposure Period	Endpoint	Acute Ni value (µg/m^3)
Ni and inorganic Ni compounds	Texas Commission Environmental Quality (TCEQ)	1 hour	Elicitation of asthma among occupational asthmatics	Acute ReV: 1.1
Ni and Ni compounds Nickel oxide	Office of Environmental Health Hazard Assessment (OEHHA)	1 hour	Immunotoxicity	Acute REL: 0.2
Ni (withdrawn from website for review)	Agency for Toxic Substances and Disease Registry (ATSDR)	1 to 14 days	Respiratory irritation	Acute MRL: 0.1
Ni and Ni compounds	Minnesota Department of Health (MDH)	1 hour	Respiratory irritation	Acute HRV02: 11
Ni compounds and metallic Ni	Quebec Ministry of the Environment	24 hour	Lung toxicity in 90-day study	MELCC: 0.07
Ni carbonyl	National Research Council (NRC)	8 hour	Severe pulmonary effects in mice	AEGL 2 (disabling):4,500 (no AEGL 1 set)

Objective

Develop an inhalation reference concentration (RfC) for 24-hour acute exposure to nickel protective of public health for use in state air toxics programs.

Methods

1. Review data from authoritative sources and the scientific literature to determine sensitive Points of Departure (PODs) for acute exposures. Sources reviewed included:
   - ATSDR 2024 Toxicological Profile
   - OEHHA 2012 Nickel Reference Exposure Levels
   - TCEQ 2017 Nickel and Inorganic Nickel Compounds
   - NRC 2008 Nickel Carbonyl Acute Exposure Guideline Levels

   PODs included previously determined LOAELs, NOAELs and BMDLs from animal and human studies.
2. Develop dose adjustment factors (DAFs) to account for differences in dosimetry between animals and humans using the multiple-path particle dosimetry (MPPD) model,
3. Apply time adjustment factors to calculate Human Equivalent Concentrations (HECs), and
4. Apply appropriate uncertainty factors.

Results

POD Selection

Buxton et al. (2021) was selected as the basis for the POD for an acute (24-hour) RfC. This study administered nickel chloride by whole-body exposure for 24 hours and provided a no-observed-adverse effect level (NOAEL) of **0.081 mg/m^3**, which was the delivered dose for the 0.1 mg/m^3 dose group.

- The Buxton et al. (2021) study followed the EPA OPPTS 870.7800 test guideline for immunotoxicity, was GLP compliant, and provided exposure particle size data allowing for interspecies dose extrapolation.
- There was no decreased immune activity response at the highest dose.
  - Dose selection for the 24-hour test administration was based on the 2-hour LOAEL and NOAEL derived by Graham et al. (1978), which was extrapolated to 24-hour exposures following Haber's Rule.
  - Nickel doses included 0, 0.02, 0.05, and 0.1 mg/m^3 and a positive control group exposed to cyclophosphamide (CP).
- Host T-cell antibody immunological responses to IV-injected sheep red blood cells were measured ex vivo in an Antibody-Forming Cell (AFC) assay.
  - No immunosuppression was observed in terms of total spleen activity, specific activity, or decreased weight of the spleen and thymus or body weight. Significant effects were observed for the positive control.
  - Decreased spleen cell count was observed at the highest dose but attributed to natural variability of outbread mice by the authors. NOAEL for spleen cell count was 0.044 mg/m^3.

Dose Adjustment Factor (DAF)

To calculate the DAF, the MPPD model was run for the mouse and the human to estimate an HEC for the NOAEL of (0.081mg/m^3) in Buxton et al. (2021). Most input parameters are automatically calculated in MPPD model. The DAF is calculated as:

$$\text{DAF} = \left(\frac{\text{Human BW}}{\text{Mouse BW}}\right) \times \left(\frac{\text{Mouse Ventilation rate}}{\text{Human Ventilation rate}}\right) \times \text{(Total Fractional Deposition)}$$

- MPPD only has two options for a mouse model species (BALB/c and B6C3F1); however, CD-1 mice were used in the Buxton et al. (2021) study. Thus, model runs were made with assumptions for both mouse species for comparison.
- MPPD has several lung model options for humans. Three of those were run: Yeh/Schum Symmetric, Yeh/Schum 5 Lobe, and Stochastic (60th percentile). The human values for tidal volume and breathing frequency were consistent with previous EPA Integrated Risk Information System (IRIS) reviews.

Using these different modeling options, numerous DAFs and HECs for the POD (POD_{HEC}) were determined (**Table 3**). The findings were reasonably consistent, resulting in DAFs ranging from 3.45 to 5.43, and a median POD_{HEC} was 0.318 mg/m^3.

No time adjustment factors are needed because the exposure duration matches the acute 24-hour duration of the RfC value.

Reference Concentration (RfC) for Acute 24-hour Ni Exposures

The RfC was derived by dividing the median POD_{HEC} (0.318 mg/m^3) by standard intra- and inter-species uncertainty factors of 10 for human sensitivity (UF_H) and 3 for animal to human difference in toxicodynamics (UF_A).

$$\text{RfC} = \frac{\text{POD}_{\text{HEC}}}{\text{UF}_\text{H} \times \text{UF}_\text{A}} \qquad \text{RfC} = \frac{0.318\ \text{mg/m}^3}{10 \times 3}$$

The resulting RfC for acute 24-hour exposures is **0.011 mg/m^3 or 11 µg/m^3**.

Table 2. Possible PODs for 24-hour acute exposure periods1

Study	Exposure Duration/Species	NOAEL (mgNi/m^3)	LOAEL (mgNi/m^3)	Outcome	Comment
Animal Studies					
Adkins et al., 1979	2 hours 80-160 F Mice (CD-1)	0.37	0.5	Decreased macrophage activity and increased susceptibility	
Benson et al., 1995	1,2,4,7, 12 days, 6 hours/day 4-6 M&F Rats (F-344)	0.44 Body Weight	0.44 Respiratory	BW NOAEL: 0.44 (7 days) Respiratory LOAEL 0.44 (7 days)	Alveolitis LOAEL due to nickel subsulfide, not relevant for ambient exposures
Buxton et al., 2021	24 hours, whole body exposure, 10-15 F Mice (CD-1)	0.081 No effect immune activity 0.044 For decreased spleen cell count	0.081 Decreased spleen cell count	Immune response to sRBCs, no effect on immune response or spleen weight	Authors conclude 0.081 NOAEL for immune function
Efremenko et al., 2017	5 days, 6 hours/day 5 M Rats (F-344)	0.06 (total protein and LDH in BALF)	0.11 (inc. total protein and LDH in BALF) 0.22 (inc. LDH and total protein in BALF) Minimal – mild bronchiole degeneration and hyperplasia	Respiratory effects	LOAEL for bronchiole degeneration of 0.22 selected as POD for ATSDR Acute MRL (now withdrawn). Only dose assessed for pathology.
Graham et al., 1978	2 hours 14-29 F Mice (Swiss)	0.1	0.25	Immune-impaired response to sRBCs	Selected as POD for OEHHA Acute (1-hour) REL, BMDL: 0.165
Human Studies					
Cirla et al., 1985	30 min 12 M&F occupational asthmatics in Ni plating	–	0.67 Only dose administered	>15% decreased FEV_1 in sensitized workers	Selected POD for TCEQ acute (1-hour) ReV

[1]Possible PODs limited to studies reporting NOAELs or LOAELs for exposures less than or equal to 6 hours/day for 5 days
F=female, M=male, GLP =good laboratory practice, OPPTS = Office of Prevention, Pesticides and Toxic Substances, sRBCs=sheep red blood cells

Table 3. DAFs and HECs for Buxton et al. (2021) NOAEL

Mouse model used:	BALB/c Model			B6C3F1 Model		
Human model used:	Yeh/Schum Symmetric	Yeh/Schum 5 Lobe	Stochastic (60th percentile)	Yeh/Schum Symmetric	Yeh/Schum 5 Lobe	Stochastic (60th percentile)
DAFs						
VE ratio – using VE ratio from MPPD output	3.66	3.71	3.71	3.45	3.50	3.50
VE ratio – using EPA values – mouse 0.052 m^3/day	5.35	5.42	5.43	5.04	5.12	5.12
VE ratio – using EPA values – mouse 0.039 m^3/day	4.01	4.07	4.07	3.78	3.84	3.84
POD_{HEC} (mg/m^3)						
POD_{HEC} – using VE ratio from MPPD output	0.296	0.300	0.300	0.279	0.283	0.283
POD_{HEC} – using EPA VE values – mouse 0.052 m^3/day	0.433	0.439	0.439	0.408	0.414	0.414
POD_{HEC} – using EPA VE values – mouse 0.039 m^3/day	0.325	0.329	0.330	0.306	0.310	0.311
Median POD_{HEC} (mg/m^3)	**0.318**					

Discussion

The RfC developed herein for acute 24-hour exposures is based on a NOAEL for immunotoxicity recently published in the high-quality study by Buxton et al. (2021), which used a guideline study design and was GLP compliant. It is also ideal for this purpose because the exposure period matches that of the acute RfC (24-hours), and thus no time adjustments are necessary to extrapolate from short exposures (e.g., 30 minutes to 2 hours) or repeated intermediate exposures (e.g., 6 hours/day for 5 days per week). Further, the study provides sufficient data to allow for the determination of a DAF and HEC, reducing the need for an uncertainty factor accounting for interspecies differences in toxicokinetics.

The ATSDR (2024) Toxicological Profile, which is no longer available online, concluded that the lowest LOAELs for respiratory and immunotoxicity were similar.

- LOAEL: 0.25 mg/m^3 for immunological effects reported in Graham et al. (1978)
- LOAEL: 0.22 mg/m^3 for respiratory effects reported in Efemenko et al. (2017).

However, these studies used different test species, and durations of exposure.

- The Graham et al. (1978) study exposed mice once for 2 hours, and the Efemenko et al. (2017) study exposed rats for 6 hours per day for 5 days.
- ATSDR selected the Efemenko et al. (2017) study because it provided the lowest LOAEL for respiratory effects, regardless of the difference in exposure durations; however, the duration of the Efemenko et al. (2017) study is more akin to the definition of acute used by ATSDR for MRLs of 1-14 days.
- The inconsistency between the LOAEL from Graham et al. (1978) (0.25 mg/m^3 for 2 hours or 0.5 mg/m^3-hr) and the NOAEL from Buxton et al. (2021) (0.081 mg/m^3 for 24 hours or 1.9 mg/m^3-hr), which both used the same strain of mice, indicates that immune effects do not strictly follow the Haber Rule, at least for the deposited dose levels of these studies, or there are other inconsistencies in these PODs as discussed by Buxton et al. (2021).

It is important to establish that the Buxton et al. (2021) NOAEL of 0.081 mg/m^3 for immunotoxicity is also protective of respiratory effects.

- Efremenko et al. (2017) studied genomic and respiratory effects following exposure to nickel sulfate hexahydrate for 6 hours per day, 5 days per week for 1 and 4 weeks. In the more relevant 1-week exposure group (30 total hours of exposure), the authors reported that BMDs were more sensitive (lower) for immune effects as compared to those related to morphogenesis, reflective of tissue damage and repair.
- Efremenko et al. (2017) also reported that immune signaling was down regulated at week 1, but not different from controls at week 4, and that Cox2 expression, which is a key genomic element of acute inflammatory response, was substantially increased (15-fold) at week 1.
- Efremenko et al. (2017) reported a NOAEL and LOAEL for total protein and LDH in BALF (**Table 2**) of 0.06 and 0.11 mg/m^3, respectively. These values are similar to the NOAEL of 0.087 mg/m^3 for immunotoxicity, although the differences in species, and thus potential differences in deposited dose, and in exposure durations, should be considered.
- Using the Regionally Deposited Dose Ratio (RDDR) calculated by ATSDR (2024) of 0.77 for the Efremenko et al. (2017) study, the $NOAEL_{HEC}$ based on the rat NOAEL that was reported for total protein and LDH in BALF (0.06 mg/m^3) is 0.046 mg/m^3, and approximately four times higher than the 24-hour RfC based on the NOAEL for immunotoxicity reported in the Buxton et al. (2021), supporting its health protectiveness for both respiratory and immune effects.

The 24-hour RfC for acute effects of 0.011 mg/m^3 (11 µg/m^3) is higher than those developed by TCEQ and OEHHA for 1-hour exposures; however, these guidelines were developed prior to conduct of the Buxton et al. (2021) study, and in the case of OEHHA's REL, a cumulative 1000-fold uncertainty factor was applied to the POD from Graham et al. (1978), which results in a much lower value than the acute RfC proposed here, which required a smaller 30-fold uncertainty factor.

Conclusion

The acute 24-hour RfC for nickel of 11 µg/m^3 is well supported and should be considered for use in state air toxics regulatory programs, including those in Minnesota, Oregon and Texas, as guidance values for 24-hour exposures, because an appropriate 24-hour value has not previously been available.

Acknowledgement and Disclosure: This work was conducted for Stoel Rives, LLP.

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ATTACHMENT B

ToxStrategies Phosgene TRV Memo

ToxStrategies

Innovative solutions
Sound science

Technical Memorandum

March 25, 2026

To:	J.R. Giska and Apollonia Goeckner, Oregon Department of Environmental Quality; Holly Dixon, PhD, Oregon Health Authority
From:	Deborah Proctor and Chad Thompson, ToxStrategies LLC
Subject:	**Evaluation of Draft Proposed Updates to Phosgene TRVs for Cleaner Air Oregon**

To support the current review of the inhalation toxicity reference values (TRVs) used in the Cleaner Air Oregon (CAO) program, we have evaluated the current (chronic) and proposed (acute) TRVs that Oregon Department of Environmental Quality (ODEQ) and Oregon Health Authority (OHA) have presented to the Air Toxics Science Advisory Committee (ATSAC) for its consideration for phosgene. This memorandum discusses in more detail the proposed phosgene acute TRV and current chronic phosgene TRV. **Table 1** below briefly summarizes our conclusions and recommendations, which are discussed in more detail in this memorandum.

Table 1. Summary of recommendations for proposed updates to phosgene TRVs

ODEQ Current or Proposed TRVs (µg/m^3)	Recommendations for Updates to Proposed TRV
Current Chronic TRV 0.3	The chronic TRV is based on the U.S. EPA Reference Concentration (RfC) developed in 2005 using a rat inhalation study (Kodavanti et al. 1997). Since then, significant additional research has been conducted as summarized and further analyzed in Pauluhn (2021) to generate a more scientifically defensible point of departure (POD) protective of both edema- and hypoxia-related outcomes. This POD is approximately 10 times higher than that developed by EPA. Applying the same uncertainty factors as EPA, use of the POD from Pauluhn (2021) results in a recommended chronic TRV of 5 µg/m^3.
Proposed Acute TRV 0.17	The acute TRV for phosgene is based on a 1-hour Reference Exposure Level (REL) published by the California Office of Environmental Health Hazard Assessment (OEHHA) divided by 24 hours/day. This REL is quite dated, being last updated by OEHHA in 1999, and since that time, toxicology research related to phosgene has expanded significantly. Newer research includes phosgene exposure studies for longer periods (e.g., 4 hours/day), which provide more relevant PODs for developing a 24-hour value based on a 1-hour exposure. Based on the current and rigorous research of Pauluhn (2021), supported by other recent studies, we recommend that ODEQ propose an acute TRV of 16 µg/m^3.

Current Research

Significant additional research has been conducted to better characterize the inhalation toxicity of phosgene since OEHHA and EPA developed acute (1 hour) and chronic inhalation toxicity criteria, which provide the basis for the proposed acute and current chronic TLVs for phosgene herein. These studies provide several additional important points for consideration when developing TRVs for phosgene. These include:

- Earlier studies, including the study used by OEHHA to set the acute REL (Dillar et al. 1985), described effects in the lung that are non-adverse adaptive responses to phosgene exposure. These include turnover of pulmonary surfactant, macrophage accumulation, and alveolitis in the absence of parenchymal pathologies or increased lung weight (Pauluhn 2021).
- Acute NOAELs are indistinguishable from those in longer term studies (Pauluhn et al. 2007). This is consistent with EPA's RfC derivation in which effects were

approximately equal, or slightly less severe at 12 weeks as compared to 4 weeks of exposure. As such, EPA applied a 3-fold uncertainty factor for extrapolation from the POD to a chronic exposure.

- Repeat exposure effects appear to be dependent on the threshold daily exposures. The threshold based on an increased protein in BALF following a single exposure was essentially identical to the concentration and duration product from subchronic exposure in rats. Thus, the chronic outcome appears to be contingent on the acute pulmonary threshold dose (Pauluhn et al. 2008).
- Rats are significantly more sensitive to the effects of phosgene than dogs or humans. Dogs are approximately three to four times less susceptible to phosgene than rats under similar exposure conditions (Pauluhn et al. 2008). Humans have an approximately 7-fold larger pool volume of alveolar macrophages than rats, which affords a higher capacity for recycling pulmonary surfactant (Pauluhn 2021, 2011b; Pauluhn et al. 2006 a, b,c; Dillar et al. 1985). The POD developed by Pauluhn (2021) is based on data for rats and dogs combined and is more relevant to humans than relying solely on rat data.

Research conducted by Pauluhn and colleagues indicates that lung weight following phosgene exposure integrates pulmonary edema-related fluid accumulation leading to acute lung injury. Pauluhn (2021) demonstrated that phosgene-induced increases in relative lung weight are best explained by the product of concentration (C) and duration of exposure (t) than exposure concentration (see **Figure 1**). Pauluhn modeled these data and derived a 95% lower confidence limit on the benchmark concentration (BMCL) for relative lung weights in rats and dogs exposed acutely to phosgene of 455 mg/m^3-min. This BMCL was interpreted as indicating that lung weight following phosgene exposure will increase when the C × t product is ~455 mg/m^3-min. Pauluhn (2021) noted that this value was consistent with a similar endpoint reported in rats exposed to 0.81 mg/m^3 for 6 h/day 5 d/wk for 12 wk in Kodavanti et al. (1997)[1], i.e., ~295 mg/m^3-min. Pauluhn further concluded that "…chronic outcomes are dependent on the acute threshold…The mode of action typical of phosgene generates acute NOAELs that are almost indistinguishable from what is observed in longer-term inhalation studies (Pauluhn et al. 2007)." Based on these data, Pauluhn (2021) proposed an updated occupational exposure level (OEL) for phosgene. Herein, we use these analyses to support derivation of updated chronic and acute TRV values as described below.

[1] Kodavanti et al. (1997) was used as the basis of the EPA chronic RfC.

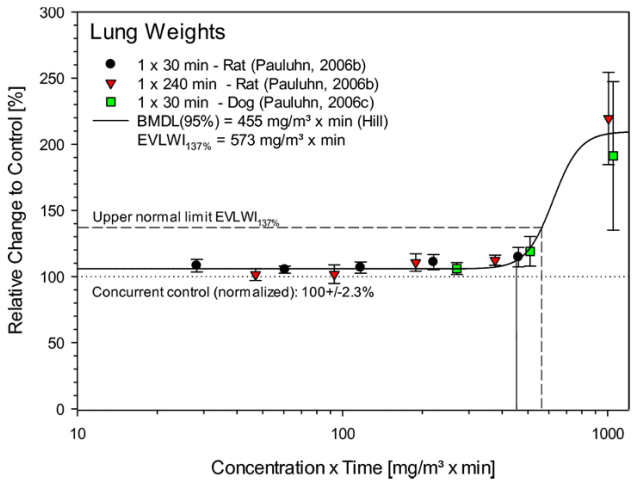

Figure 1. Dose-response relationship between relative lung weight changes in rats and dogs and acute exposure to phosgene. Source: Pauluhn (2021; Figure 6)

Current Chronic TRV

The EPA RfC of 0.3 µg/m^3 is the current chronic TRV. EPA (2005) notes that studies of animals are limited to short term exposures and in the study used as the basis of the RfC (Kodavanti et al. 1997), effects were more severe at 4 weeks than 12 weeks of exposure. The more current research of Pauluhn (2006 a,b,c; 2011a,b; 2021) improves upon the data and knowledge to develop TRVs.

As previously discussed, Pauluhn (2021) derived a C × t POD of 455 mg/m^3-min for changes in relative lung weight indicative of lung toxicity. Pauluhn extrapolated this value to an OEL by using a rat-to-human dosimetric adjustment factor (DAF) and applying uncertainty factors (discussed further below). A similar approach was used herein to derive a chronic TRV. Specifically, Pauluhn's C × t POD of 455 mg/m^3-min equates to a 24-hour concentration of 0.32 mg/m^3-day (455 mg/m^3-min ÷ 1440 min). Using the same rat-to-human DAF as EPA (2005), i.e., a regional gas dose ratio to the thoracic region ($RGDR_{TH}$) of 1.5, the 0.32 mg/m^3-day equates to a human equivalent concentration (HEC) of 0.47 mg/m^3 (0.32 mg/m^3 x 1.5). Applying a 3-fold interspecies uncertainty factor (UF_A), 10-fold human variability factor (UF_H), and retaining the same 3-fold subchronic-to-chronic uncertainty factor (UF_S) applied in EPA (2005) results in a chronic TRV of 0.005 mg/m^3 (0.47 mg/m^3 ÷ 100[2]) or 5 µg/m^3 rounded. As such, an updated chronic TRV of **5 µg/m^3** is proposed, and we recommend that ODEQ assess this proposal in consultation with ATSAC

[2] Conventionally, 3 × 10 × 3 = 100 instead of 90 in risk assessment.

By comparison, Pauluhn (2021) proposed an 8-hour OEL of 0.8 mg/m^3 or 800 µg/m^3. Much of the difference between the Pauluhn OEL and the proposed chronic TRV is driven by differences in uncertainty factors applied (3 vs 100) and exposure duration (8 vs 24 hours).

Proposed Acute TRV

As discussed in the previous section, Pauluhn's C × t POD of 455 mg/m^3-min equates to a 24-hour value of 0.32 mg/m^3-day (455 mg/m^3-min ÷ 1440 minutes). Using the same $RGDR_{TH}$ DAF of 1.5 as applied in EPA (2005), equates to a human equivalent concentration (HEC) of 0.47 mg/m^3 (0.32 mg/m^3 x 1.5). As discussed in Pauluhn (2021), humans have an ~7-fold higher alveolar macrophage pool responsible which protects against phosgene toxicity, as compared to that in rats, suggesting that humans are more resistant to phosgene toxicity as compared to rats. Nevertheless, applying a 3-fold UF_A for toxicodynamic uncertainties and a 10-fold UF_H for potential human variability results in an acute TRV of 0.016 mg/m^3 (0.47 mg/m^3 ÷ 30) or 16 µg/m^3. This acute TRV differs from the chronic TRV due to the application of a 3-fold UF_S in the latter. This is consistent with Pauluhn (2021):

> "As is typical for such a mode of action, integrated toxicity occurs based on the C ×t of the exposure day rather than the frequency of exposure days…. The mode of action typical of phosgene generates acute NOAELs that are almost indistinguishable from what is observed in longer-term inhalation studies (Pauluhn et al., 2007)."

Since the repeat dose toxicity is related to the acute threshold, the acute and chronic PODs are identical (0.32 mg/m^3), whereas the acute and chronic TRV derivations differ due to the application of uncertainty factors. While the acute and chronic TRVs might reasonably be set equal to one another, the additional 3-fold UF_S for the chronic TRV seems prudent. It should also be noted that the 3-fold UF_A applied in both the acute and chronic TRVs could be set to 1 based on evidence that humans have ~7-fold higher pool of alveolar macrophages as compared to rats. In fact, Pauluhn (2021) included only a 3-fold uncertainty factor in the OEL derivation, which was said to account for repeated exposures. Overall, we recommend that an acute TRV of **16 µg/m^3** be set by ODEQ, in consultation with ATSAC, based on this newer and more robustly investigated research.

To further assess whether this acute TRV is sufficiently protective, we benchmarked this estimate against empirical data closer to a 24-hour exposure scenario. Specifically, the 240-minute acute rat data in the Pauluhn (2021) analysis (see **Figure 1**) were obtained from Pauluhn (2006 b)[3] and modeled in BMDS v25.1 as a function of concentration instead of C × t. The resulting $BMCL_{10}$ value was 0.61 mg/m^3. Adjusting the 4-hour exposure to 24

[3] The lowest exposure dose was excluded because the actual chamber concentration was higher than target concentration.

hours results in a duration-adjusted $BMCL_{10}$ of 0.10 mg/m^3 (0.62 mg/m^3 x 4/24). This $BMCL_{10}$ is remarkably close to the estimated C × t POD of 0.32 mg/m^3-day. Bearing in mind that rats appear to be more sensitive to phosgene than dogs and humans (Pauluhn, 2021), this duration-adjusted BMCL is overly conservative.

Comments on the Proposed ODEQ TRVs

It is important to note that many phosgene studies discuss effects as a function of concentration as well as concentration times exposure duration (C x t). However, some studies (e.g., Kodavanti et al. 1997) include repeat dosing in these calculations whereas Pauluhn (2021) expresses C x t as a daily dose. For example, Kodavanti et al. (1997), which is the basis of the EPA RfC and chronic TRV, expresses exposure to 0.2 ppm for 6 h/day, 5 d/wk for 12 wk as a C x t of 72 ppm-hr (0.2 ppm × 6 h × 5 days × 12 weeks). Converting ppm to mg/m^3 and hours to minutes, this equates to 17,565 mg/m^3-min (0.813 mg/m^3 × 360 min × 5 days × 12 weeks). However, when specifically referring to this exposure scenario from Kodavanti et al. (1997), Pauluhn (2021) calculates the daily C x t as 295 mg/m^3-min (0.813 mg/m^3 × 360 min).[4] Pauluhn (2012) argues that toxicity is initiated at a threshold dose upon first exposure. Because phosgene interacts with proteins and lipids in surfactant, adaptive responses to phosgene exposure results in increased surfactant synthesis in type II pneumocytes as well as surfactant turnover mediated by alveolar macrophages. Exposures that overwhelm this adaptive response can lead to tissue damage and inflammatory responses. Thus, consistent with the observations of Kodavanti et al. (1997), observed effects are lessened upon extended duration of exposure.

As discussed in Pauluhn (2021), dogs are more resistant to phosgene-induced lung injury, and the dog lung is more similar to humans than rodents. As such, the daily C x t threshold for pulmonary edema (as indicated by relative lung weight) calculated using both rat and dog lung data provides a better estimate of daily exposure threshold than rats alone, which are the bases of both the acute and chronic phosgene TRVs. Notably, the Pauluhn (2021) estimate of 455 mg/m^3-min daily threshold based on relative increases in lung weight is comparable (within ~1.5 fold) to similar changes in Kodavanti et al. (1997). It is also similar to the 0.1 ppm (equal to 147 mg/m^3-min) group in Kodavanti et al. (1997) where collagen staining was reported. As such, it is likely that protection against pulmonary edema (as measured as increased lung weight) is protective against subsequent toxicities such as fibrosis given the higher sensitivity of rats to phosgene compared to dogs and humans. As such, the chronic TRV proposed above, while higher than the EPA RfC, is scientifically robust.

As for the proposed acute TRV, it is notable that the POD for the proposed acute and chronic values are the same (0.32 mg/m^3-day)—consistent with the notion of a daily exposure threshold for toxicity. The difference in the proposed acute and chronic TRVs is

[4] The exact number depends on rounding assumptions. We calculate 293 mg/m^3-min using the measured phosgene chamber concentration (0.201 mg/m^3) and conversion of mg/m^3 = ppm × 98.92/24.45.

the application of uncertainty factors (see above). Oddly, the ODEQ proposed acute TRV is *lower* than the chronic value which is biologically illogical. ODEQ proposes to take a 1-hour REL value developed by OEHHA and divide it by 24 as a form of C x t adjustment. The OEHHA value itself, based on data in Diller et al. (1985), is based on the absence of "lesions" in rats exposed to 0.1 ppm phosgene for 1 hour. The lesion in question appears to be the presence of foamy cells at ≥4 hours of exposure but not 1 hour of exposure. The foamy cells are presumed to be surfactant-based lipid inclusions in alveolar macrophages, which are adaptive responses due to macrophage recycling of phosgene-damaged surfactant (Pauluhn 2021). At the 4 hour exposure (250 minutes specifically), no changes in BALF were reported (Dillar et al. 1985). Thus, the presence of foamy cells in other exposure groups is not necessarily adverse, but an adaptive response. Rats exposed to 0.1 ppm for 500 min (8.3 h) also exhibited slight (~2-fold) increases in protein in bronchial lavage fluid (Diller et al. 1985); however, the biological relevance of this mild increase is not known (Pauluhn 2006 a).

Diller et al. (1985), the basis of the acute TRV, did not report incidence data for histopathological observations (via light or electron microscopy) thereby precluding statistical or dose-response analyses. Moreover, the interval between exposure and necropsy was 48 hours for all treatment groups except the controls and the 1-hour exposure to 0.1 ppm phosgene, thereby confounding various interpretations from the study as it is known that responses following exposure to phosgene change between 24 and 72 hours post exposure (Pauluhn 2021). It is nevertheless notable that the OEHHA's NOAEL of 0.1 ppm (~0.4 mg/m^3) for their 1-hr REL is comparable to the POD of 0.37 mg/m^3 proposed based on the research of Pauluhn (2021). ODEQ's proposal to divide the OEHHA REL of 4 μg/m^3 by 24 resulting in 0.17 μg/m^3 is not scientifically defensible as evidenced, in part, by the fact that the acute value would be lower than the chronic value. Furthermore, adjusting the NOAEL of 0.1 ppm by 24 results in 0.004 ppm. The lowest exposure dose in the subchronic study by Dillar et al. (1985) and Kodavanti et al. (1997) was 0.1 ppm, suggesting there is likely no empirical data to support a POD of 0.004 ppm.

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ATTACHMENT C

ToxStrategies Presentation on Blood Lead

Novel Application of the EPA All Ages Lead Model (AALM) to Determine an Acute (24-hour) Inhalation Threshold for Lead Protective of Neurotoxicity in Children

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Abstract #: 4604 Poster #: E379

Objectives

Using the U.S. EPA's AALM, develop an acute (24-hour) health-based inhalation threshold for Pb in ambient air that is protective of a 1 µg/dL increase in blood lead among potentially exposed male and female children, while accounting for lead exposure by other pathways.

Background

- Many state air toxics regulatory programs require inhalation reference criteria protective of acute (24-hour) exposures as part of risk assessment of air toxics. Such a guideline is challenging to determine for lead (Pb), as the most sensitive endpoint is neurotoxicity associated with increased blood Pb in children, and risk assessment typically involves blood lead modeling of longer-term exposures and multiple exposure pathways.
- One approach is to use the National Ambient Air Quality Standard (NAAQS) for Pb of 0.15 µg/m^3, which is currently used by the Oregon Department of Environmental Quality (ODEQ) as the acute exposure criterion.
- However, the NAAQS is intended for a 3-month average concentration, as opposed to the 24-hour duration of an acute criteria, and thus is not well suited to characterize 24-hour exposures.
- We developed an alternative approach to setting an acute threshold for Pb, using the EPA's All Ages Lead Model (AALM) Version 3.1 (EPA 2025), which allows users to simulate single-day exposures.
- Biokinetic modeling was performed to predict the air concentration for one day of exposure that would result in a blood Pb increase of 1 µg/dL. The California Office of Environmental Health Hazard Assessment (OEHHA) uses this as the threshold for source-specific incremental increase in blood lead levels (BLLs) for protection of school children and fetuses (OEHHA, 2007).

Methods

- EPA's AALM was used to estimate BLLs for children (0-6 years) each year because children are more sensitive than adults, and kinetic and exposure parameters change as children grow.
- First, baseline BLLs were modeled considering all exposure routes in the AALM (e.g., soil, indoor dust, food) except for air, using default model inputs (EPA, 2024).
- The maximum upper tolerance limit for Pb in Oregon soil of 79 µg/g was used for modeling soil and dust exposures.
- The AALM was subsequently run in an iterative process by changing the air concentration on a single day until the estimated BLLs corresponded to a BLL of 1 µg/dL above baseline. The single day of exposure (i.e., acute pulse) was simulated separately for each year from year 0 to year 6, such that there were seven different model simulations.
- To simulate an acute, 24-hour exposure scenario for one age group, the air concentration was assumed to be 0 µg/m^3 except for the single day of exposure for the age group of interest. This value was assumed to allow for pulsed exposure in the model, but as shown by the results of the pulsed modeling, the default air concentration for Pb (0.01 µg/m^3) does not contribute significantly to BLLs.
- The AALM uses masks to set exposures for specific repeating periods. In this case, an annual mask was set to 0 µg/m^3 for days 2 through 365 of each year. Day 1 exposure was set to 0 µg/m^3 for all age groups except for the specific age group with the acute 24-hour exposure by changing the model's grouping of age groups for each simulation. The year with acute/pulsed exposure had a non-zero air concentration. For example, for year 1, the air concentrations on day 1 were modeled in three age groups: (1) age 0 at 0 µg/m^3, (2) age 1 at the non-zero air concentration, and (3) age 2 at 0 µg/m^3, which then continued from age 2 through the end of the simulation (6.1 years).
- Default lung parameters from AALM 3.0 were selected (EPA 2024, 2025). These parameters represent lung kinetics for ultra-fine (approximately 0.1 µm in diameter) combustion aerosols, and relative bioavailability for inhalation exposure was assumed to be 1 (EPA, 2024).

Results

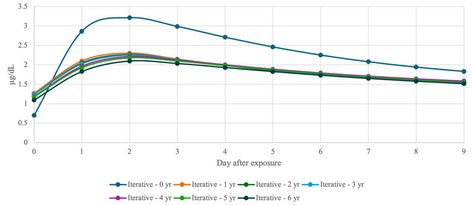
- Baseline BLLs ranged from 1.10-2.21 µg/dL (**Table 1**).

Table 1. Baseline and target BLL

Age (in Years)	Day	Baseline BLL µg/dL)	Target BLL (µg/dL)
0	2	2.21	3.21
1	367	1.30	2.30
2	732	1.27	2.27
3	1097	1.25	2.25
4	1462	1.21	2.21
5	1827	1.18	2.18
6	2192	1.10	2.10

- AALM predicted that the highest BLL following acute air exposures occurs on the third day of the year (i.e., two days after exposure) (**Figure 1**).

Figure 1. Predicted BLLs for each age group following exposure



- The single-day air concentration that resulted in a predicted BLL closest to the target increased the BLL range from 3.86 µg/m^3 (year 0) to 7.64 µg/m^3 (year 5) (**Table 2**). These values are all well above the 3-month average NAAQS for Pb of 0.15 µg/m^3.
- The most sensitive age group was newborn (0-1 year age group), and the 24-hour airborne Pb concentration associated with a 1 µg/dL increase from the baseline BLL was 3.9 µg/m^3 (**Table 2**).

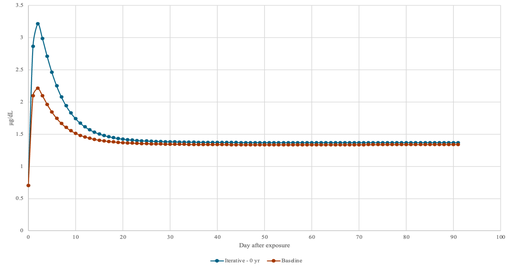
Table 2. Iterative air concentrations and BLL

Year	Day	Baseline BLL (Day 2) (µg/dL)	Target BLL (µg/dL)	Single day air concentration[1] (µg/m^3)	Predicted BLL (µg/dL)
0	2	2.21	3.21	3.86	3.21
1	367	1.30	2.30	5.80	2.30
2	732	1.27	2.27	6.84	2.27
3	1097	1.25	2.25	6.83	2.25
4	1462	1.21	2.21	7.31	2.22
5	1827	1.18	2.18	7.64	2.18
6	2192	1.10	2.10	7.01	2.10

[1]U.S. EPA's default ambient air concentration for AALM (0.01 µg/m^3) is 0.3% of the pulsed air concentration and would not contribute significantly to BLL relative to the pulsed exposure.

- Only the predicted BLL for the 4-year age group was slightly higher (0.01 µg/dL) than the target BLL, but the results for the 4-year old age group were higher (less conservative) than those for the 0-year age group (**Table 2**).
- The estimated BLLs decreased to baseline BLLs within approximately 20 days, and the peak BLL was 3.21 µg/dL, which is lower than the CDC reference level of 3.5 µg/dL (**Figure 2**).

Figure 2. Baseline and pulsed iterative BLLs between year 0 and year 1



Conclusions

- Assuming background exposures to lead in soil, dust and diet, an acute 24-hour threshold for Pb in ambient air of 3.9 µg/m^3 would be protective for all ages, including children.
- This guideline is complementary to the NAAQS because a single pulsed 24-hour concentration of 3.9 µg/m^3 would not exceed the NAAQS when averaged with background Pb in air concentrations (i.e., 0.01 µg/m^3) over three months.

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Keywords (3)
Lead (Pb); toxicity reference value (TRV); biokinetic modeling

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