Oregon Department of Environmental Quality

PFAS Toxicity

PFAS 2025 Rulemaking

Introduction

This memo is provided to support the commission in finding that the proposed per- and poly-fluoroalkyl substances (PFAS) may pose a present or future hazard to human health, safety, welfare or the environment. ORS 465.400 (3) states the commission may designate hazardous substances by rule after finding "that the substance, because of its quantity, concentration, or physical, chemical or toxic characteristics, may pose a present or future hazard to human health, safety, welfare or the environment should a release occur." This memo summarizes the research and reports documenting the toxic characteristics of the PFAS compounds proposed in the PFAS 2025 rulemaking, including perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), hexafluoropropylene oxide dimer acid (HFPO-DA or GenX), perfluorobutane sulfonic acid (PFBS). Additional PFAS compounds with toxicity data available are also discussed, including perfluorobutanoic acid (PFBA), perfluorodecanoic acid (PFDA), perfluoroheptanoic acid (PFHpA), perfluorohexanoic acid (PFHxA), and perfluoropropanoic acid (PFPrA).

Health effects are summarized by the U.S. Environmental Protection Agency's (EPA) toxicity assessments, which are prepared by the Health and Ecological Criteria Division and Integrated Risk Information System within the Center for Public Health and Environmental Assessment. The U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR) also provides toxicological profiles for PFAS (ATSDR, 2021). The toxicity reviews on health effects are used to support the development of criteria protective of drinking water consumption (EPA, 2024a), fish consumption (EPA. December 2024 a and b), and exposure to environmental media at contaminated sites by developing regional screening levels (RSLs). PFAS occur in mixtures, and evidence supports dose-additive effects from combined exposure to multiple PFAS. Several PFAS (e.g., PFNA, GenX, PFBS) have been shown to elicit the same or similar adverse effects including those on thyroid hormone levels, lipid synthesis and metabolism, development, immune system function, and liver function (ATSDR, 2021; EFSA, 2018, 2020; EPA, 2021a, 2021b). Dose additivity means that combined effected of the chemicals in the mixture is equal to the sum of the individual doses or concentrations scaled for potency. Therefore, EPA established a framework for estimating noncancer health effects associated with mixtures of PFAS substances (EPA, April 2024).

Environmental effects have been established through EPA's Office of Water, Science and Technology Health and Ecological Criteria Division. In 2024, EPA finalized chronic and acute aquatic life criteria for PFOA and PFOS to provide information that states and Tribes may consider for establishing water quality standards under the Clean Water Act. The development of national recommended ambient water quality criteria (AWQC) establishes criteria for the protection of freshwater and saltwater species such as fish, invertebrates, plants, amphibians, and reptiles in water and whole body and muscle tissue (invertebrates and fish) (EPA September 2024 a and b). Additionally, EPA developed acute freshwater benchmarks for eight data-limited PFAS including PFBA, PFHxA, PFDA, PFBS, PFHxS, 8:2 FTUCA, and 7:3 FTCA (EPA, September 2024c). These eight PFAS were selected based on input from interested parties and the availability of aquatic test data. While PFOA and PFOS are the most studied PFAS, the development of chronic criteria was precluded due to missing toxicity data for one or more representative families of aquatic organisms.

This memo is not comprehensive but focuses on presenting a summary of health effects with the strongest evidence, including those for which effects have been quantified. Human health effects are summarized below; however, additional information related to ecological impacts is not provided.

Background on PFAS Health Effects

Many PFAS and/or their degradation products exhibit high persistence in the environment. This is due to the carbon-fluorine bond, which is particularly strong, stable, and resistant to degradation in the environment (mineralization, abiotic) or animal tissue (metabolic). These PFAS then accumulate in food (e.g., plant produce, fish tissue, agricultural meat and milk) via soil and water. PFAS bind to proteins in the body, which efficiently distributes PFAS into different tissues and across brain and placental barriers, and results in the accumulation in protein-rich organs like the liver. Increasing chain length (from C6 to C11) correlates with an increased mass in blood plasma. Several PFAS trigger adverse effects at low concentrations in organs such as the liver or immune system, are suspected human carcinogens, and cause harm to the developing child through transmission to unborn and breastfeeding children. Cumulative adverse effects from multiple PFAS compounds occur because they share similar chemical structures and modes of action that cause common health effects across different levels of biological organization, tissues / organs, life stages, and species (ATSDR, 2021; EFSA et al., 2018, 2020).

Exposure to PFAS have been linked to several adverse health effects, described in more detail by system below.

Liver

PFAS binding to proteins triggers molecular and cellular effects on organs such as the liver. These pathways are associated with PFAS-induced liver injury after exposure to perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), PFHxS, PFNA, and perfluorodecanoic acid (PFDA) in EPA Integrated Risk Information System Assessments (EPA, 2021), and cancer for PFOS (EPA, 2021). The liver is a primary target for long-chain PFAS storage. The following is an outline of molecular, cellular, and organ effects resulting in liver disease:

- Molecular activation of signaling pathways that regulate lipid metabolism (e.g., PPAR-α and PPAR-γ, CAR/PXR)
- Altered lipid cholesterols, triglycerides, glucose metabolism, inflammation, and oxidative stress
- Increased damage to liver cells (hepatocytes) responsible for bile formation, production of proteins, carbohydrate transformation, and the breakdown and excretion of chemicals
- Direct effects on liver including necrosis, fatty acid accumulation, and serum enzymes
- Metabolic effects including diabetes, gestational diabetes, insulin resistance, weight gain, and metabolic syndrome

Cardiovascular

Cardiovascular effects are a result of an increase in blood lipids (cholesterol) from PFAS protein binding and activation, as described above. This results in increased blood pressure and the build-up of fats, cholesterol, and plaque in the artery walls (atherosclerosis). This may result in an increased risk of heart attack and stroke.

Immune System

PFAS can alter immune cells and signaling, which results in reduced antibody production and immunity. This has been tested by evaluating the immune response to vaccinations in laboratory and epidemiological studies.

The adverse health effects associated with PFAS exposure on the immune system are listed below:

- Decreased vaccine response – reduced antibody production
- Altered spleen and thymus weights
- Increased susceptibility to infectious diseases

- Increased incidence of autoimmune disorders caused by dysregulated immune-inflammatory pathways, such as gastroenteritis, irritable bowl disease, and Crohn's disease
- Hypersensitivity and increased histamine response (asthma, allergy, atopic dermatitis)

Kidney

The kidneys are a site of PFAS enrichment resulting from the circulation of plasma proteins in the body and its role in excretion and reabsorption (Shearer et al, 2021). PFAS, particularly long chained compounds, are efficiently reabsorbed into the body as a part of the kidney's role in conserving useful solutes (typically glucose, amino acids, and phosphates) before excretion. This maintains PFAS in circulation and increases exposure to other organs.

Kidney injuries occur through induction of cell death, fibrosis, oxidated stress, inflation, genetic changes, and metabolic disruptions. PFAS exposure has been linked to kidney cancer, chronic kidney disease, renal fibrosis, inflammation, changes in kidney function markers such as urine creatinine and albumin ratios, and the formation of kidney stones (Hanvoravongchai et al., 2024).

Endocrine

PFAS interact with thyroid hormone binding proteins, causing the disruption of thyroid hormones, in particular decreases in T4. Thyroid hormones regulate metabolism by, for example, ensuring that the liver processes fats in the blood. During fetal development and through early childhood, thyroid hormones play an important role in growth and development, immune function (Rivera et al., 2024, Funes et al., 2022), and cognitive function (Korevaar et al., 2016, Haddow et al., 1999).

The adverse health effects associated with PFAS exposure on the thyroid are listed below:

- Increase in total and high-density lipoprotein cholesterol because thyroid hormones ensure liver cells remove excess cholesterol
- PFAS, particularly PFOA, dysregulate hormone levels in liver cells that produce thyroid hormone transport proteins, resulting in a reduction in thyroid hormones T3 and free T4
- Binding directly to serum thyroid hormone transport proteins, blocking the transport of T4 in the body
- Increase in thyroid gland weight due to low thyroid hormone levels
- Maternal health and development and increase in premature birth, preeclampsia, and miscarriage
- Decrease in T4 has been shown to result in low fetal weight and poor neurological development
- Reduction in IQ scores, elevated risk of autism spectrum disorders and other neurodevelopmental disorders

Pancreas

Effects on the pancreas from PFAS exposure are related to its role in secreting digestive enzymes and hormones to aid in regulating blood sugar. PFAS binding interferes with metabolic process that regulate cell growth and energy use, leading to insulin resistance, pancreatic tumor formation and cancer development (Kamendulis et al., 2022, Caverly et al., 2014).

Reproductive and Developmental

PFAS have been associated with impacts on reproductive hormones, reproduction rate, and reduction in semen volume, sperm count, and motility. PFAS have also been found to accumulate in fetal tissues in the placenta, cord blood, and amniotic fluid, and transfer from nursing parents to their infants via breastmilk. PFAS exposure is associated with changes in birth size, gestational duration, birth defects, developmental effects, placental effects and fetal loss. The degree of distribution has been found to vary by gestational age and

duration of breastfeeding. Distribution is influenced by the chemical properties of the PFAS including length, lipophilicity, and branching. PFAS are linked to increased incidence of cancers of the testicles and breast.

PFAS Proposed for Rulemaking

Federal agencies such as EPA and the Agency for Toxic Substances and Disease Registry rigorously evaluate human epidemiological studies and experimental animal-based exposure studies to identify high quality studies for calculating toxicity values. These quantitative toxicity values have been calculated for the six PFAS in this proposed rulemaking. Quantitative toxicity values include reference doses (RfDs) for non-cancer effects, and cancer slope factors (CSFs) for cancer effects. RfDs are estimates of daily exposure to the population that is likely to be without an appreciable lifetime risk of non-cancer effects, such as organ damage, biochemical, physiological, or pathologic changes and death. Chemicals may elicit more than one toxic effect (endpoint) and, as such, may have several RfDs.

For cancer effects, EPA first evaluates the weight of evidence for a chemical to cause cancer. CSFs are then developed if sufficient carcinogenicity data are available. A slope factor is an estimate of the probability of a response per unit intake of a chemical over a lifetime. The higher the CSF, the more potent a chemical in causing cancer. Non-cancer effects can be developed for all chemicals, while CSFs are only developed for carcinogens. Therefore, some chemicals may have both RfDs and CSFs. It is important to note that many of the health effects are cumulative, or additive, when mixtures of PFAS are present.

Summaries of the toxicity of PFAS compounds proposed for rulemaking are provided below.

PFOA toxicity

PFOA is a long-chain (8 carbon) PFAS compound that has been used in many consumer and industrial products to provide resistance to heat, stains, grease and water. For example, PFOA has been used in carpets, rugs, furniture, non-stick cookware and firefighting foams. After exposure, PFOA preferentially accumulates in platelets, and can be found at highest levels in plasma bound to proteins, followed by whole blood and serum (De Toni et al., 2020). EPA concluded that there is evidence from both epidemiological and animal toxicological studies to determine that oral PFOA exposure may result in adverse health effects across many health outcomes, including cancer (EPA, 2024). Exposure to PFOA has been linked with the following adverse effects:

- Cancer (Kidney, teste, liver and pancreatic)
- Immune effects, based on decreased immune response to tetanus and diphtheria vaccines
- Developmental effects including decreased infant birth weight, and survival
- Cardiovascular effects including increased total cholesterol and LDL and increased blood pressure
- Elevated enzymes associated with liver damage and cell death

There was significant information to develop RfDs based on immune anti-tetanus and diphtheria response (Budtz-Jorgensen and Grandjean, 2018; Timmerman et al., 2021), decreased immune response (Dewitt et al., 2008), decreased birth weight (Chu et al., 2020; Sagiv et al., 2018, Starling et al., 2017, Wikström et al, 2020), decreased offspring survival and delayed time to eye opening (Song et al., 2018, Lau et al., 2006), liver necrosis (NTP, 2020), cardiovascular effects increased total cholesterol (Dong et al., 2019, Steenland et al., 2009) andelevated enzymes reflective of liver damage (Gallo et al, 2012, Darrow et al, 2016, Nian et al, 2019). The overall RfD is based on the immune, developmental (birth weight), and cardiovascular health outcomes.

EPA determined that there is significant information to determine a quantitative association between PFOA exposure and development of cancer. Cancer slope factors were developed for kidney (Shearer et al., 2021), teste (Butenhoff et al., 2012), liver (NTP, 2020), and pancreatic (NTP, 2020) cancer. Other cancers associated with PFOA exposure include uterine (NTP, 2020) and breast (Mancini et al., 2020, Ghisari et al., 2017). The

final toxicity value for cancer was based on kidney cancer. The International Agency for Research on Cancer classified PFOA as Group 1 carcinogenic to humans (Zahm et al., 2024).

PFOS toxicity

PFOS is a long-chain (8 carbon) PFAS compound that has been used in many consumer and commercial products as an aqueous dispersion agent and emulsifier in a variety of water, oil and stain repellent applications such as agricultural chemicals, alkaline cleaners, carpets, rugs, furniture, non-stick cookware, firefighting foam, floor polish and textiles (EPA, 2024). EPA concluded that there is evidence from both epidemiological and animal toxicological studies to determine that oral PFOS exposure may result in adverse health effects across many health outcomes, including cancer (EPA, 2024). Exposure to PFOS has been linked with the following adverse effects:

- Cancer (liver and pancreas)
- Immune effects, based on decreased immune response to tetanus, diphtheria, and rubella vaccines
- Decreased antibody production
- Increased blood and immune cell production by spleen
- Decreased fetal and infant birth weight
- Increased total cholesterol
- Elevated enzyme associated with liver cell death and damage

There were strong enough lines of evidence for EPA to develop quantitative RfDs for five immune effects, two developmental effects, one cardiovascular effect, and two liver effects for non-cancer health outcome. These include decreased immune response to tetanus, diphtheria, and rubella vaccines (Budtz-Jorgensen & Grandjean, 2018; Timmerman et al., 2021), decreased antibody production (Zhong et al., 2016), increased blood cell production in the spleen (NTP, 2019), developmental decreased fetal and infant birth weight (; Sagiv et al., 2018; Starling et al., 2017; Wikstrom et al., 2020; Darrow et al., 2013; Luebker et al., 2005), increased total cholesterol (Dong et al., 2019; Steenland et al., 2009; Lin et al., 2010), and necrosis and elevated enzyme associated with liver disease (Gallo et al., 2012; Nian et al, 2019; Butenhoff et al., 2012; Thomford, 2002). The overall RfD is based on the two strongest lines of evidence, decreased birth weight in infants (Wikstrom et al, 2020) and increased serum total cholesterol in adults (Dong et al., 2019).

EPA determined that there is significant information to determine a quantitative association between PFOS exposure and development of cancer in the liver and pancreas (Butenthoff et al., 2012; Thomford, 2002). EPA selected the liver adenomas and carcinomas reported by Butenhoff et al., 2012 and Thomford 2002 as the basis for the overall slope factor due to the concordance between observations in animal and human epidemiological studies. Though other cancers have been found associated with PFOS exposure, including those of the kidney (i.e., renal cell carcinoma), bladder, breast, prostate, ovary, and thyroid, the limited or mixed results in the literature currently preclude the quantitative assessment of data on these cancers.

The International Agency for Research on Cancer has classified PFOS as Group 2B possibly carcinogenic to humans (Zahm et al., 2024).

PFHxS toxicity

PFHxS is a long-chain (6 carbon) PFAS compound with application in many commercial and consumer products to provide resistance to heat, stains, grease, and water. For example, PFHxS has been used in carpets, textiles, electronics, cleaning and polishing products, and to make fluoropolymers. PFHxS has also been used in firefighting foams. PFHxS is often found associated with PFOS given that multiple PFHxS isomers are found as minor fractions of PFOS generated using electrochemical fluorination. Three PFHxS isomers have been identified. The most prevalent is the linear isomer (N-PFHxS), and the other two are branched isomers. Exposure to PFHxS has been linked with the following adverse effects:

- Thyroid hormone function, based on decreased T3 and T4 levels
- Immune effects, inferred from decreased antibody formation after diphtheria and tetanus vaccines administered to children
- Decreased birth weight
- Increased liver enzymes (serum ALT) which indicate damage and inflammation
- Toxicity studies evaluating exposure to multiple PFAS indicate that exposure to a mixture of PFOA, PFOS, and **PFHxS** (Marques et al., 2021), a mixture of PFOA, PFOS, PFNA, **PFHxS,** and HFPO-DA (Roth et al., 2021), or a mixture of PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFBS, **PFHxS,** and PFOS (Crute et al., 2022) produced numerous significant health effects consistent with the spectrum of individual PFAS effects (e.g., liver injury; thyroid hormone alterations)

Based on this, EPA developed two lifetime RfDs for thyroid impacts on development (Ramhøj et al., 2018) and immune endpoints (Grandjean et al, 2012; Budtz-Jorgensen & Grandjean, 2018), however EPA concluded that there are inadequate data on cancer to quantitatively assess the carcinogenic potential for PFHxS in humans. Evidence from epidemiology studies suggest PFHxS exposure might affect fetal development resulting in decreased birth weight, neurodevelopmental, liver effects, cardiovascular disease, and diabetes. However, data was limited, and toxicity values were not derived.

PFNA toxicity

PFNA is a long-chain (9 carbon) PFAS compound. In addition to general use stain resistance, PFNA was primarily used in the production of polyvinylidene fluoride (PVDF). PVDF uses include as insulators for wire, circuit boards, valves, pipes, and for protection against reactive chemicals. PFNA has also been used in children's consumer products including infant sleeping bags and sports and outdoor clothing. The EPA assessment (EPA 2024) focused on the free acid of PFNA given the currently available toxicity data but applies to non-alkali or alkali metal salts. Health effects with significant evidence include those for developmental, liver, and male reproductive effects. The EPA found inadequate information to assess the carcinogenic potential for PFNA. Exposure to PFNA has been linked with the following adverse effects:

- Thyroid and adrenal gland effects (NTP, 2018)
- Immune effects inferred from decreased antibody formation after diphtheria and rubella vaccinations in children
- Reproductive and developmental effects include decreased birth weight (male and female) (Sagiv et al., 2018), decreased survival (Das et al., 2015; Wolf et al., 2010), delays in developmental landmarks (eye opening, vaginal opening, and male sexual development) (Das et al., 2015)
- Developmental neurotoxicity including attention-deficit/hyperactivity disorder (ADHD) and related behaviors
- Male reproductive effects including decreased reproductive organ weights (testis and epididymis) (NTP, 2018), altered testosterone levels (serum and testicular), and impaired spermatogenesis.
- Increased liver enzymes (serum ALT, AST, and bilirubin), which indicates damage and inflammation (Kim et al., 2023; Nian et al., 2019), PPAR-α-induced liver toxicity, increased liver weights (NTP, 2018; Wang et al., 2015; Das et al, 2015), and lesions

GenX toxicity

GenX is a short-chain (6 carbon) PFAS compound created to replace PFOA. GenX is a trade name for a processing aid technology that enables the creation of fluoropolymers without the use of PFOA (Chemours, 2018). Toxicity data indicate multiple modes of action for toxicological effects, primarily on the liver, after exposure to GenX. RfDs were developed based on liver effects (DuPont, 2010). There is also evidence that exposure results in non-cancerous and cancerous growths in females (liver) and males (pancreas), although

there was not enough information to quantify a CSF for cancer endpoints. Exposure to GenX has been linked with the following adverse effects (EPA, 2021):

- Development of cancerous and non-cancerous growths
- Increase in the size of liver cells from enzyme induction via PPAR-α activation, liver enlargement, and liver necrosis
- Decreased red blood cell count, hemoglobin, and hematocrit (DuPont, 2008)
- Increased organ weight, tissue necrosis, and hyperplasia (uncontrolled cell growth) in the kidney
- Increased incidence of premature birth, placental lesions, and maternal gestational weight gain (Conley et al, 2019)
- Immune effects through suppression of antibody response and increased lymphocyte levels (Rushing et al., 2017)

The critical study chosen for determining RfDs was the oral reproductive/developmental toxicity based on liver effects (a constellation of lesions, necrosis, and disease) (DuPont, 2010; NTP, 2019b). Although there is limited data on carcinogenicity, DuPont studies indicated liver and pancreatic tumors, particularly at high exposure doses, and that testicular cancer could not be ruled out (DuPont, 2013).

PFBS toxicity

PFBS is a short-chain (4 carbon) PFAS compound developed as a replacement for PFOS (3M, 2002). PFBS was primarily used as a surfactant in paint manufacture, cleaning agents, and water- and stain-repellant products. There was sufficient data for EPA to derive RfDs for thyroid and kidney effects but inadequate data to derive a CSF. Exposure to PFBS has been linked with the following adverse effects:

- Decreases in total T3 and T4 and free T4 (NTP, 2019; Feng et al., 2017) and related impacts on development, reproductive and immune systems (Haddow et al., 1999; Gilbert et al., 2016; Gilbert, 2011)
- Kidney effects including hyperplasia, inflammatory changes, and abnormal cell growth (Lieder et al., 2009)
- Developmental effects including decreased BW and delayed eye opening (Feng et al., 2017)

The RfD was based on thyroid effects as decreased serum total T4 in newborns (Feng et al., 2017). Selection of total T4 as the critical effect accounts for correlations in thyroid physiology and hormone development, particularly within the context of a developmental life stage.

Additional PFAS compounds

Some compounds in addition to the six proposed in this rulemaking also have toxicity research, data, and values available, indicating these compounds may also pose a hazard to human health, safety, welfare or the environment.

PFBA toxicity

PFBA is a short-chain (4 carbon) PFAS compound. An IRIS toxicological review for PFBA was finalized in 2022 by EPA (EPA, 2022), establishing RfDs for non-cancer effects listed below. PFBA is included in ATSDR's toxicological profile (ATSDR, 2021).

- Increased liver weight and size (Butenhoff et al., 2012, Das et al., 2008)
- Increased hypertension (Bao et al., 2017)
- Thyroid impacts, observed from decreased total T4 (Butenhoff et. al., 2012)

- Embryo and fetal mortality (Das et al., 2008)
- Developmental delays, including delayed eye and vaginal opening (Das et al., 2008)

The overall RfD was selected based on developmental delays (EPA, 2022). No studies were available that evaluated carcinogenicity of PFBA precluding the derivation of quantitative estimates.

PFDA toxicity

PFDA is a long-chain (10 carbon) PFAS compound. PFDA has been used in stain and grease-proof coatings on food packaging, furniture, upholstery, and carpet (Harbison et al., 2015; Kotthoff et al., 2015). An IRIS toxicological review for PFBA was finalized in 2024 by EPA (EPA, July 2024), establishing RfDs for non-cancer effects listed below. PFBA is included in ATSDR's toxicological profile (ATSDR, 2021). PFDA induces increases in serum lipids similar to PFOA, PFOS and PFNA, and decreased antibody response to vaccines similar to PFOA, PFOS, and PFHxS (ATSDR, 2021). Inadequate information exists to evaluate carcinogenicity.

- Immune effects based on decreased serum antibody concentrations for tetanus and diptheria (Grandjean et al, 2012; Budtz-Jorgensen & Grandjean, 2018).
- Developmental impacts by evidence of decreased birth weight (Wikstrom et al, 2020)
- Increased liver weight (NTP, 2018)
- Male reproductive effects via decreased epididymis weight, a sign of testicular inflammation (NTP, 2018)
- Female reproductive effects as demonstrated by an increase in menstrual cycle length via hormonal impacts (NTP, 2020)
- Toxicity studies evaluating exposure to multiple PFAS indicate that exposure to a mixture of PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, **PFDA**, PFBS, PFHxS, and PFOS (Crute et al., 2022) produced numerous significant health effects consistent with the spectrum of individual PFAS effects (e.g., liver injury; thyroid hormone alterations)

From the RfDs developed from the effects listed above, an overall RfD was selected based on decreased serum antibody concentrations and decreased birth weight.

PFHpA toxicity

PFHpA is long-chain (7 carbon) PFAS compound and has been consistently detected in monitoring events in ambient waters, particularly where firefighting foam was used (Anderson, 2016, Ruyle et al., 2021). PFHpA is listed a substance of high concern by the European Union due to reproductive toxicity and its persistence, bioaccumulative and toxic properties. PFHpA has been determined by many states to be of sufficiently similar chemical structure to PFOA and PFOS to be considered in additivity evaluations (Maine DEP, 2021, Massachusetts DEP, 2019, Levine, 2018, VT Dec. 2021, Australia Government Dept of Health, 2019). EPA has not yet released toxicity reviews for PFHpA. Exposure to PFHpA has been linked with the following adverse effects:

- Reproductive toxicity effects, such as increased serum testosterone, luteinizing hormone, and follicle-stimulating hormones and effects on testes (Leydig cells) (Li et al., 2021).
- Toxicity studies evaluating exposure to multiple PFAS indicate that exposure to a mixture of PFOA, PFOS, and PFHxS (Marques et al., 2021), a mixture of PFOA, PFOS, PFNA, PFHxS, and HFPO-DA (Roth et al., 2021), or a mixture of PFBA, PFPeA, PFHxA, **PFHpA**, PFOA, PFNA, PFDA, PFBS, PFHxS, and PFOS (Crute et al., 2022) produced numerous significant

health effects consistent with the spectrum of individual PFAS effects (e.g., liver injury; thyroid hormone alterations)

PFHxA toxicity

PFHxA is a long-chain (6 carbon) PFAS compound. An IRIS toxicological review for PFHxA was finalized in 2023 by EPA (EPA, 2023), establishing RfDs for non-cancer effects listed below. PFHxA is included in ATSDR's toxicological profile (ATSDR, 2021).

- Liver enlargement through increased cell size (Loveless et al., 2009)
- Decreased red blood cells (hematopoietic effects) (Klaunig et al., 2015)
- Developmental decreased birth weight (Loveless et al., 2009)
- Endocrine impacts, observed via decreased free T4 (NTP, 2018)
- Toxicity studies evaluating exposure to multiple PFAS indicate that exposure to a mixture of PFBA, PFPeA, **PFHxA**, PFHpA, PFOA, PFNA, PFDA, PFBS, PFHxS, and PFOS (Crute et al., 2022) produced numerous significant health effects consistent with the spectrum of individual PFAS effects (e.g., liver injury; thyroid hormone alterations)

From the hazards identified above, decreased offspring body weight was selected as the basis if the RfD. There was inadequate information to assess carcinogenic potential.

PFPrA toxicity

PFPrA is a short-chain (3 carbon) PFAS compound and is a clear, colorless liquid. PFPrA forms from the breakdown of longer-chain PFAS and the reaction of HFPO and viny ether operations. EPA's Center for Public Health and Environmental Assessment finalized human health Rfd toxicity values for PFPrA (EPA, June 2023). Effects are consistent with PFBA, a closely related linear short-chain (4 carbon) PFAS (EPA, 2021).

- Increased liver weight, increased size of liver cells, degenerative changes, and increased serum markers of liver injury (alanine aminotransferase-ALT and alkaline phosphatase - ALP) (Duan et al., 2020, Song et al., 2018, Li et al., 2017, CERI, 2002 a, b & c).

Liver impacts formed the basis of the RfD (EPA, June 2023). There was inadequate information to assess carcinogenic potential.

Documents relied on for PFAS toxicity

Document title	Document location
ATSDR, 2021. Toxicological Profile for Perfluoroalkyls.	https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf
ATSDR, 2024. How PFAS Impacts Your Health.	https://www.atsdr.cdc.gov/pfas/about/health-effects.html
Bao WW, Qian ZM, Geiger SD, et al. 2017. Gender-specific associations between serum isomers of perfluoroalkyl substances and blood pressure among Chinese: Isomers of C8 Health Project in China. Sci Total Environ 607-608:1304-1312.	http://doi.org/10.1016/j.scitotenv.2017.07.124

Budtz-Jorgensen, E., and Grandjean, P. 2018. Application of Benchmark Analysis for Mixed Contaminant Exposures: Mutual Adjustment of Perfluoroalkylate Substances Associated with Immunotoxicity	https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0205388&type=printable
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EPA grant disclaimer

This project has been funded wholly or in part by the United States Environmental Protection Agency under assistance agreement # 44-02J54901 to Oregon Department of Environmental Quality. The contents of this document do not necessarily reflect the views and policies of the Environmental Protection Agency, nor does the Environmental Protection Agency endorse trade names or recommend the use of commercial products mentioned in this document, as well as any images, video, text, or other content created by generative artificial intelligence tools, nor does any such content necessarily reflect the views and policies of the Environmental Protection Agency.