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DEPARTMENT OF ECOLOGY
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Date: June 7, 2024

To: Donald Brown and Elizabeth Allen – EPA Region 10 Risk Evaluation Branch; Barbara Morrissey – Washington State Department of Health

From: Andy Kallus – Ecology Toxics Cleanup Program (TCP) ask

Subject: Selection of Human Health Toxicity Criteria for PFAS Chemicals

Cc: Kris Grinnell, Sarah Wollwage, Bonnie Brooks – Ecology TCP

Purpose and Background: The purpose of this memo is to provide the United States Environmental Protection Agency (EPA) Region 10 and the Washington State Department of Health (DOH) with our approach and recommendations for selecting updated human health toxicity criteria for per- and polyfluoroalkyl substances (PFAS). All acronyms used in this memo are defined in a list at the end the text, and references cited are provided after the acronym list.

In March of 2022, the Washington State Department of Ecology (Ecology) provided EPA Region 10 a briefing memo (*see* **Attachment 1**) with our approach and recommendations for selecting human health toxicity criteria for the following five PFAS substances for which DOH developed State Action Levels (SALs): PFOA, PFOS, PFNA, PFHxS, and PFBS. For these five PFAS, Ecology selected the oral reference doses (RfDs) adopted by DOH in the development of their SALs. Since this time and after finalization of the SALs, we've selected toxicity criteria for HFPO-DA (GenX Chemicals), PFBA, and PFHxA. Toxicity criteria for PFBA and PFHxA are from EPA's Integrated Risk Information System (IRIS) database (IRIS, 2024), and the criteria for HFPO-DA is from EPA's Office of Water (Health and Ecological Criteria Division) (EPA, 2021a).

In April of this year, EPA's Office of Water (Health and Ecological Criteria Division) released final toxicity assessments for PFOA and PFOS (EPA, 2024a; 2024b). EPA also set maximum contaminant levels (MCLs[1]) for the following six PFAS: PFOA, PFOS, HFPO-DA, PFBS, PFHxS, and PFNA. Of the five PFAS that we consulted on in 2022, only PFOA and PFOS have updated toxicity criteria to consider. The status of toxicity criteria selected by Ecology for the

[1] PFAS National Primary Drinking Water Regulation. 40 CFR Parts 141 and 142. EPA Final Rule. 89 Fed. Reg. 32532 (Apr. 26, 2024). Individual MCLs were established for PFOA, PFOS, HFPO-DA, PFHxS, and PFNA. In addition, the sum of the concentrations for PFBS, HFPO-DA, PFHxS, and PFNA cannot exceed a hazard index of 1. *Note that an individual MCL was not established for PFBS.*

eight PFAS in our Cleanup Levels and Risk Calculations (CLARC) databased is summarized below.

- **PFOA** – DOH selected the Agency for Toxic Substances and Disease Registry (ATSDR) intermediate minimal risk level (MRL[2]) of 3E-06 mg/kg-day as the basis for development of its SAL for PFOA (DOH, 2021). As provided in our March 2022 memo (*see* **Attachment 1**), Ecology selected the ATSDR PFOA MRL for deriving Model Toxics Control Act (MTCA) cleanup levels. In April of this year, EPA's Office of Water issued a final toxicity assessment for PFOA that recommended a more stringent (i.e., lower) chronic oral RfD and determined that it's "likely to be carcinogenic to humans via the oral route of exposure" (EPA, 2024a).

  Additional discussion is included herein to document our recommendation for selecting EPA's Office of Water toxicity criteria for PFOA.

- **PFOS** – In concurrence with the Minnesota Department of Health (MDH) and the New Hampshire Department of Environmental Services (NHDES), DOH selected a toxicity study based on immune effects as the basis for development of its SAL for PFOS (MDH, 2019a; NHDES, 2019). This resulted in the derivation of a chronic RfD of 3E-06 mg/kg-day. As provided in our March 2022 memo (*see* **Attachment 1**), Ecology selected this RfD for deriving MTCA cleanup levels for PFOS. In April of this year, EPA's Office of Water issued a final toxicity assessment for PFOS that recommended a more stringent (i.e., lower) chronic oral RfD and determined that it's "likely to be carcinogenic to humans via the oral route of exposure" (EPA, 2024b).

  Additional discussion is included herein to document our recommendation for selecting EPA's Office of Water toxicity criteria for PFOS.

- **HFPO-DA** – Ecology added HFPO-DA to CLARC in August 2022 and currently uses the EPA Office of Water chronic oral RfD of 3E-06 mg/kg-day to derive MTCA cleanup levels (EPA, 2021a).

  Since this PFAS was not included in the March 2022 consultation, additional discussion is included herein to document our selection of EPA's Office of Water toxicity criteria for HFPO-DA.

- **PFBS** – DOH selected EPA's 2021 chronic oral RfD Provisional Peer-Reviewed Toxicity Value (PPRTV) of 3E-04 mg/kg-day for the development of their PFBS SAL (DOH, 2021; EPA, 2021b). Ecology selected this RfD for deriving MTCA cleanup levels for PFBS. EPA PPRTV toxicity criteria are included in MTCA's hierarchy of toxicity sources (*see* discussion on toxicity hierarchy in **Attachment 1**) and EPA uses the PFBS PPRTV RfD in their Superfund Program.

  No further toxicity criteria updates have been identified for PFBS. **Attachment 1** contains additional discussion for this PFAS substance.

[2] An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are analogous to RfDs.

- **PFBA** – Ecology added PFBA to CLARC in January 2023 and currently uses the EPA IRIS chronic oral RfD of 1E-03 mg/kg-day to derive MTCA cleanup levels (IRIS, 2024). EPA IRIS toxicity criteria are included in MTCA's hierarchy of toxicity sources (*see* discussion on toxicity hierarchy in **Attachment 1**) and EPA uses the PFBA RfD in their Superfund Program.

  No further toxicity criteria updates have been identified for PFBA and no additional discussion is provided herein.

- **PFHxS** – The EPA Superfund Program uses the ATSDR intermediate MRL of 2E-05 mg/kg-day (ATSDR, 2021) for calculating PFHxS regional screening levels (RSLs). Since the ATSDR MRL was first derived (in 2018), newer high-quality studies on PFHxS have become available (DOH, 2021). Rather than using the ATSDR MRL, DOH selected the MDH chronic RfD of 9.7E-06 mg/kg-day for the development of their SAL (DOH, 2021; MDH, 2019b). Ecology selected this RfD for deriving MTCA cleanup levels for PFHxS. A toxicity assessment is currently under draft development (Step 4 of 7) for PFHxS by EPA's IRIS Program.

  No further toxicity criteria updates have been identified for PFHxS. **Attachment 1** contains additional discussion for this PFAS substance.

- **PFHxA** – Ecology added PFHxA to CLARC in August 2023 and currently uses the EPA IRIS chronic oral RfD of 5E-04 mg/kg-day to derive MTCA cleanup levels (IRIS, 2024). EPA IRIS toxicity criteria are included in MTCA's hierarchy of toxicity sources (*see* discussion on toxicity hierarchy in **Attachment 1**) and EPA uses the PFHxA IRIS RfD in their Superfund Program.

  No further toxicity criteria updates have been identified for PFHxA and no additional discussion is provided herein.

- **PFNA** – The EPA Superfund Program uses the ATSDR intermediate MRL of 3E-06 mg/kg-day (ATSDR, 2021) for calculating PFNA RSLs. DOH also selected the ATSDR intermediate MRL for development of its SAL. However, DOH modified the MRL slightly by incorporating updated half-life information for PFNA. This yielded a slightly more conservative oral RfD of 2.5E-06 mg/kg-day which Ecology selected for deriving MTCA cleanup levels for PFNA. A toxicity assessment is currently under draft development (Step 4 of 7) for PFNA by EPA's IRIS Program.

  No further toxicity criteria updates have been identified for PFNA. **Attachment 1** contains additional discussion for this PFAS substance.

Human Health Toxicity Criteria Updates for PFAS Chemicals: We have determined that EPA's Office of Water toxicity criteria developed for PFOA, PFOS, and HFPO-DA provide an appropriate basis for establishing cleanup levels under MTCA. The toxicity studies that form the basis of the Office of Water toxicity criteria are high quality, peer-reviewed, comprehensive, and based on current EPA guidelines for risk assessment including their Office of Research and Development (ORD) Staff Handbook for Developing IRIS Assessments (EPA, 2022, 2014, 2012, 2011, 2002). EPA's Office of Water toxicity criteria for PFOA, PFOS, and HFPO-DA are summarized below.

- **Perfluorooctanoic acid (PFOA)** – Toxicity data for PFOA is not available from any of the toxicity sources identified in the MTCA Rule (*see* discussion on toxicity hierarchy in **Attachment 1**).

  Current Toxicity Value. Since March of 2022, we have been using ATSDR's intermediate MRL of 3E-06 mg/kg-day to calculate MTCA cleanup levels. ATSDR based its intermediate MRL of 3E-06 mg/kg-day on a developmental study using mice (published in 2016) that generated a lowest-observed-adverse-effect level (LOAEL) of 0.3 mg/kg-day and an estimated maternal serum (blood) level of 8.29 mg/L—based on developmental effects in mouse offspring in adulthood following gestational exposure (Koskela et al. 2016; ATSDR, 2021).

  New EPA Toxicity Assessment – In April 2024, EPA through its Office of Water issued a final toxicity assessment for PFOA, including all isomers and nonmetal salts (EPA, 2024a). This toxicity assessment was peer reviewed by the EPA Science Advisory Board (SAB) and conducted consistent with the methodology outlined in ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022).

  EPA assembled a database of epidemiological, animal toxicological, mechanistic, and toxicokinetic studies for this PFOA toxicity assessment which included the assessment by ATSDR (ATSDR, 2021). Literature screening was conducted consistent with the IRIS Handbook (EPA, 2022) and the *Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments* (EPA, 2020).

  - Candidate RfDs – Based on evidence from both human epidemiological and animal toxicological studies, EPA concluded that oral exposure to PFOA can result in adverse health effects across a range of health outcomes. The strongest overall weight of evidence linking oral exposure to PFOA to noncancer health outcomes are based on effects to the following noncancer organs/systems: immune, cardiovascular, hepatic, and developmental. As such, EPA derived and considered multiple candidate RfDs based on these noncancer effects.

    EPA followed agency guidelines and methodologies for risk assessment in determining points of departure (PODs) for the derivation of the RfDs for PFOA (EPA, 2022, 2014, 2012, 2011, 2002). EPA performed benchmark dose modeling following EPA's *Benchmark Dose Technical Guidance Document* to derive BMDLs[3] (EPA, 2012). For data from animal toxicological studies, when BMDLs could not be derived, EPA used a no-observed-adverse-effect level/lowest-observed-adverse-effect level (NOAEL/LOAEL) approach.

    Studies selected for PFOA by EPA included those that had sufficient data to model serum level across the dose-range. That is, internal dose (serum level) rather than the external dose (administered dose) was used to represent the POD (i.e., POD Internal). After POD derivation, EPA used a pharmacokinetic model for human dosimetry to estimate human equivalent doses (HEDs) from both animal and epidemiological studies. This modelling resulted in a chronic dose

[3] A BMDL is the lower limit of the 95 percent confidence interval on the benchmark dose (BMD). BMDs are derived based on a pre-defined target called a benchmark response (BMR). The BMR is a specified change in response for an effect relative to its background response rate (e.g., 10% increase in liver lesions. In this case it's a dichotomous response—the presence or absence of an effect).

(POD_{HED}) that would result in the internal dose POD (i.e., POD Internal) obtained from dose-response modeling (e.g., BMDL, NOAEL/LOAEL). To calculate the candidate RfD values, EPA applied uncertainty factors (UFs) to the POD_{HEDs} derived from selected epidemiological and animal toxicological studies. UFs were applied according to methods described in EPA's *Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002).

EPA derived candidate RfDs based on both epidemiological and animal toxicological studies. Candidate RfDs derived from epidemiological studies were all within one order of magnitude of each other (1E-08 to 1E-07 mg/kg/day) regardless of endpoint, health outcome, or study population. Candidate RfDs derived from animal toxicological studies were up to three orders of magnitude higher than candidate RfDs derived from epidemiological studies.

EPA noted that there is greater uncertainty associated with the use of animal toxicological studies compared to human epidemiological studies which have greater relevance to human exposure. EPA's IRIS Handbook states that "animal studies provide supporting evidence when adequate human studies are available, and they are considered to be the studies of primary interest when adequate human studies are not available" (EPA, 2022). As a result, EPA determined that the candidate RfDs based on the animal toxicological studies would not be further considered for selection of the overall RfD.

Candidate RfDs derived from epidemiological studies (six studies that ranged from medium to high confidence) for health outcomes associated with the immune, developmental, and cardiovascular organs/systems all came out to be the same (i.e., 3E-08 mg/kg-day), and lower than the candidate RfD based on hepatic effects (2E-07 mg/kg-day; based on three medium confidence studies). **As a result, EPA selected an overall RfD for PFOA of 3E-08 mg/kg-day**. A composite UF of 10 was used to derive the chronic RfD of 3E-08 mg/kg-day. For the selected RfD, critical effects associated with each organ/system include decreased serum anti-tetanus and anti-diphtheria antibody concentrations in children (immune), decreased birth weight (developmental), and increased serum total cholesterol (cardiovascular).

- Cancer Slope Factor (CSF[4]) Selection – EPA identified and evaluated 28 epidemiological and 5 animal toxicological studies that investigated the association between PFOA and cancer. Consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2005), EPA reviewed the available data and conducted a weight of the evidence evaluation across the human epidemiological, animal toxicological, and mechanistic studies and concluded that PFOA is *Likely to Be Carcinogenic to Humans* via the oral route of exposure (EPA, 2024a). Epidemiological studies provided evidence of kidney and testicular cancer in

[4] The CSF is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential carcinogen. It's expressed as risk per unit dose or risk per mg/kg-day or $(mg/kg\text{-}day)^{-1}$.

humans and some evidence of breast cancer in a study of one susceptible subpopulation (i.e., in specific genotype or estrogen receptive groups of participants). Animal toxicological studies in Sprague-Dawley rats reported Leydig cell tumors (LCT), pancreatic acinar cell tumors (PACT), and hepatocellular tumors after chronic oral exposure.

Studies assessing mutagenicity following PFOA exposure were primarily negative, and EPA concluded that PFOA is unlikely to be carcinogenic via a mutagenic mode of action (MOA). Therefore, EPA does not recommend applying age-dependent adjustment factors (ADAFs) when quantitatively determining the cancer risk for PFOA.

Quantitation of cancer risk as a CSF was conducted consistent with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* and EPA's IRIS Handbook (EPA, 2005; EPA, 2022). EPA derived and considered multiple candidate CSFs from both epidemiological and animal toxicological studies across multiple tissue and organ types (i.e., kidney, liver, pancreas, testes). Only high or medium confidence human epidemiological and animal toxicological studies were considered for CSF derivation.

For epidemiological data, candidate CSFs were derived for several kidney cancer tumor types. The Shearer et. al. (2021) study measured effects specifically for renal cell carcinoma (RCC), a type of kidney cancer. The Vieira et al. (2013) study measured effects for any type of kidney cancer (i.e., the critical effect is kidney cancer). The model used by EPA involved a linear regression between PFOA exposure and cancer relative risk to estimate the dose-response between PFOA and RCC or kidney cancer risk. Relative risks were then converted to the absolute risk scale, yielding an internal CSF, which represents the excess cancer risk associated with each ng/mL (same as µg/L) increase in serum PFOA. The internal serum CSF was then divided by the selected clearance value and converted to an external dose CSF.

For animal toxicological studies, multistage cancer models were used to predict the doses at which the selected benchmark response (BMR) for tumor incidence would occur (i.e., 4% or 10% increase in tumor incidence). BMDLs for each tumor type (LCTs, hepatocellular adenoma or carcinoma, and pancreatic acinar cell adenoma or adenocarcinoma) served as the PODs (POD internal dose), which were then converted to POD_{HEDs} by applying the human clearance value. CSFs were then calculated by dividing the selected BMR by the POD_{HEDs} for each tumor type.

As with the candidate RfDs, EPA focused on the CSFs derived from the epidemiological data which is consistent with recommendations in the IRIS Handbook (EPA, 2022). EPA selected the critical effect of renal cell carcinomas (RCC) in human males reported by Shearer et al. (2021) as the basis of the overall CSF for PFOA. It was selected over the CSF derived for kidney cancer (Vieira et al., 2013) due to its multiple study design considerations. Also, the outcome measured for the Shearer et. al. (2021) study was for a specific type of kidney cancer (i.e., RCC vs. any kidney cancer) and the study used measured serum of

PFOA (vs. modeled in the Vieira et al. 2013 study). **The resulting overall CSF for PFOA based on RCC is 29,300 (mg/kg-day)$^{-1}$**. It's noted that he CSF for RCC is about 7 times more potent (i.e., higher and more conservative) than the CSF of 4,011 (mg/kg-day^{-1}) derived for the general kidney cancer endpoint (Vieira et al., 2013).

EPA Status. In April of this year, EPA finalized a National Primary Drinking Water Regulation (NPDWR) for six PFAS substances. Under the NPDWR, EPA established a Maximum Contaminant Level (MCL) of 4 ng/L (also expressed as parts per trillion [ppt]) for PFOA. EPA set the Maximum Contaminant Level Goal (MCLG) for PFOA at zero because of its carcinogenicity. Both MCLs (for carcinogens and noncarcinogens) and MCLGs (for noncarcinogens) are identified as Applicable or Relevant and Appropriate Requirements (ARARs) under MTCA (*see* WAC 173-340-720(3)(b)). In May of this year, EPA updated its RSL tables which included updated toxicity criteria for PFOA based on the April 2024 EPA Office of Water toxicity assessment (EPA, 2024a). EPA May 2024 RSLs for PFOA have been calculated using the EPA Office of Water derived toxicity criteria which includes an oral RfD of 3E-08 mg/kg-day and an oral CSF of 29,300 (mg/kg-day)$^{-1}$.

- **Perfluorooctane sulfonic acid (PFOS)** – Toxicity data for PFOS is not available from any of toxicity sources identified in the MTCA Rule (*see* discussion on toxicity hierarchy in **Attachment 1**).

  Current Toxicity Value. Since March of 2022, we have been using an RfD of 3E-06 mg/kg-day derived by the Minnesota Department of Health (MDH, 2019a) and the New Hampshire Department of Environmental Services (NHDES, 2019) based on immune effects to adult male mice as reported in the Dong et al. 2011 study. This is the same RfD used by DOH to derive their SAL of 15 ng/L (or ppt) for PFOS.

  New EPA Toxicity Assessment – In April 2024, EPA through its Office of Water issued a final toxicity assessment for PFOS, including all isomers and nonmetal salts (EPA, 2024b). This toxicity assessment was peer reviewed by the EPA SAB and conducted consistent with the methodology outlined in EPA's ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022).

  EPA assembled a database of epidemiological, animal toxicological, mechanistic, and toxicokinetic studies for this PFOS toxicity assessment which included the assessment by ATSDR (ATSDR, 2021). Literature screening was conducted consistent with the IRIS Handbook (EPA, 2022) and the *Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments* (EPA, 2020).

  - Candidate RfDs – Based on evidence from both human epidemiological and animal toxicological studies, EPA concluded that oral exposure to PFOS can result in adverse health effects across a range of health outcomes. The strongest overall weight of evidence linking oral exposure to PFOS to noncancer health outcomes are based on the following noncancer organs/systems: immune, cardiovascular, hepatic, and developmental. As such, EPA derived and considered multiple candidate RfDs based on these noncancer effects. Note that these are the same noncancer health outcomes that were identified and evaluated for PFOA.

EPA followed agency guidelines and methodologies for risk assessment in determining PODs for the derivation of the RfDs for PFOS (EPA, 2022, 2014, 2012, 2011, 2002). EPA performed benchmark dose modeling following EPA's *Benchmark Dose Technical Guidance Document* to derive BMDLs (EPA, 2012). For data from animal toxicological studies, when BMDLs could not be derived, EPA used a NOAEL/LOAEL approach.

Studies selected for PFOS by EPA included those that had sufficient data to model serum level across the dose-range. That is, internal dose (serum level) rather than the external dose (administered dose) was used to represent the POD (i.e., POD Internal). After POD derivation, EPA used a pharmacokinetic model for human dosimetry to estimate HEDs from both animal and epidemiological studies. This modelling resulted in a chronic dose (POD_{HED}) that would result in the internal dose POD (i.e., POD Internal) obtained from dose-response modeling (e.g., BMDL, NOAEL/LOAEL). To calculate the candidate RfD values, EPA applied UFs to the POD_{HEDs} derived from selected epidemiological and animal toxicological studies. UFs were applied according to methods described in EPA's *Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002).

EPA derived candidate RfDs based on both epidemiological and animal toxicological studies. As with PFOA, candidate RfDs derived from epidemiological studies were all within one order of magnitude of each other (1E-07 to 7E-07 mg/kg/day), regardless of endpoint, health outcome, or study population. Candidate RfDs derived from animal toxicological studies were up to three orders of magnitude higher than candidate RfDs derived from epidemiological studies. Based on the same rationale as discussed prior for PFOA, EPA determined that the candidate RfDs based on the animal toxicological studies would not be further considered for selection of the overall RfD.

Candidate RfDs derived from epidemiological studies (five studies that ranged from medium to high confidence) for health outcomes associated with the developmental and cardiovascular organs/systems came out to be the same (i.e., 1E-07 mg/kg-day), and lower than the candidate RfDs based on hepatic and immune effects (2E-07 mg/kg-day; based on five medium confidence studies). **As a result, EPA selected an overall RfD for PFOS of 1E-07 mg/kg-day**. A composite UF of 10 was used to derive the chronic RfD of 1E-07 mg/kg-day. For the selected RfD, critical effects associated with each organ/system include decreased birth weight (developmental) and increased serum total cholesterol (cardiovascular).

- <u>CSF Selection</u> – EPA identified and evaluated 17 epidemiological and 1 animal toxicological study that investigated the association between PFOS and cancer. Consistent with EPA's Guidelines for Carcinogen Risk Assessment (EPA, 2005), EPA reviewed the available data and conducted a weight of the evidence evaluation across the human epidemiological, animal toxicological, and mechanistic studies and concluded that PFOS is *Likely to Be Carcinogenic to Human*s via the oral route of exposure (EPA, 2024b). Epidemiological studies provided evidence of bladder, prostate, liver, kidney, and breast cancers in humans, although evidence was limited or mixed for some cancer types. Animal toxicological studies in Sprague-Dawley rats reported hepatocellular tumors, pancreatic islet cell tumors, and thyroid follicular cell tumors after chronic oral exposure.

Studies assessing mutagenicity following PFOS exposure were primarily negative and therefore, EPA concluded that PFOS is unlikely to be carcinogenic via a mutagenic mode of action (MOA). Therefore, EPA does not recommend applying ADAFs when quantitatively determining the cancer risk for PFOS.

Quantitation of cancer risk as a CSF was conducted consistent with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* and EPA's IRIS Handbook (EPA, 2005; EPA, 2022). EPA determined that data from epidemiological studies were not suitable for CSF derivation. Some of the epidemiological studies resulted in limited (e.g., kidney) or mixed (e.g., breast, bladder, prostate) evidence about the relationship between PFOS exposure and cancer outcomes in humans—this limited the potential for quantitative assessment of the data. Further, a medium confidence study on liver cancer was determined to not be suitable for CSF derivation in part because it lacked a precise estimate of the slope needed for POD determination.

EPA derived and considered multiple candidate CSFs based on one high confidence animal toxicological study on male and female Sprague Dawley rats across multiple organ/tumor types (i.e., liver and pancreas) (Butenhoff et al., 2012; Thomford, 2002[5]). Multistage cancer models were used to predict the doses at which the selected BMR for tumor incidence would occur (i.e., 10% increase in tumor incidence). BMDLs for each tumor type (i.e., hepatocellular adenomas or carcinomas and pancreatic islet cell carcinomas) served as the PODs (POD internal dose), which were then converted to POD_{HEDs} by applying the human clearance value. CSFs were then calculated by dividing the selected BMR by the POD_{HEDs} for each tumor type.

EPA selected the critical effect of combined hepatocellular adenomas and carcinomas in female rats as the basis of the overall CSF for PFOS. **The resulting overall CSF for PFOS based on this endpoint is 39.5 (mg/kg-day)$^{-1}$**. CSFs for the other three endpoints ranged from 29.9 (mg/kg-day)$^{-1}$ (pancreatic islet cell carcinomas) to 35.8 (mg/kg-day)$^{-1}$ (heptacellular adenomas).

EPA Status. In April of this year, EPA finalized a National Primary Drinking Water Regulation (NPDWR) for six PFAS substances. Under the NPDWR, EPA established an MCL of 4 ng/L (or ppt) for PFOS. EPA set the MCLG for PFOS at zero because of its carcinogenicity. Both MCLs (for carcinogens and noncarcinogens) and MCLGs (for noncarcinogens) are identified as ARARs under MTCA (*see* WAC 173-340-720(3)(b)). In May of this year, EPA updated its RSL tables which included updated toxicity criteria for PFOS based on the April 2024 EPA Office of Water toxicity assessment (EPA,

[5] Butenhoff et al. (2012) and Thomford (2002) reported data from the same experiment.

2024b). EPA May 2024 RSLs for PFOS have been calculated using the EPA Office of Water derived toxicity criteria which includes an oral RfD of 1E-07 mg/kg-day and an oral CSF of 39.5 $(mg/kg\text{-}day)^{-1}$.

- **Hexafluoropropylene Oxide Dimer Acid (HFPO-DA) –** Toxicity data for HFPO-DA is not available from any of toxicity sources identified in the MTCA Rule (*see* discussion on toxicity hierarchy in **Attachment 1**).

  Current Toxicity Value. Ecology added HFPO-DA to CLARC in August 2022 and currently uses the EPA Office of Water chronic oral RfD of 3E-06 mg/kg-day to derive MTCA cleanup levels (EPA, 2021a). This PFAS was not included in the March 2022 consultation (*see* **Attachment 1**). Additional discussion is provided below to document our recommendation for selecting EPA's Office of Water toxicity criteria for HFPO-DA.

  In October 2021, EPA through its Office of Water issued a final toxicity assessment for HFPO-DA and its ammonium salt (collectively known as "GenX" chemicals) (EPA, 2021a). Prior to finalization, this toxicity assessment underwent EPA agency review by multiple Program Offices including Regions 1 through 10, and two external independent expert peer reviews as well as public review and comment. The assessment was conducted using the same EPA guidelines and methodologies for risk assessment as was used in the toxicity assessments for PFOA and PFOS (*see* references EPA, 2014, 2012, 2011, 2002).

  EPA assembled a database of animal toxicological, mechanistic, and toxicokinetic studies for the HFPO-DA toxicity assessment; no epidemiological studies on health effects in humans were available. Literature screening was conducted consistent with the then draft 2020 IRIS Handbook (EPA, 2020; reference for the final document).

  - Candidate RfDs – Based on evidence from the toxicological studies reviewed, EPA found that oral exposure to GenX chemicals can result in adverse health effects across a range of health outcomes. These include the following noncancer organs/systems: hepatic, hematological, immune, and reproductive/developmental. Data from available studies indicate that the liver is the most sensitive target of toxicity from exposure to GenX chemicals. Liver effects were observed in both male and female mice and rats at varying durations of exposures and doses. Liver effects are also the endpoints that are observed at the lowest doses for GenX chemicals. As such, EPA derived and considered multiple candidate RfDs based on noncancer liver effects.

    The critical study selected for determining candidate RfDs for GenX chemicals was the oral reproductive/developmental toxicity study in mice with a NOAEL of 0.1 mg/kg-day based on liver effects (a constellation of lesions, including cytoplasmic alteration, hepatocellular single-cell and focal necrosis, and hepatocellular apoptosis) in females (DuPont-18405-1037, 2010; NTP, 2019). This study was characterized as being high quality by EPA.

    Standard guidelines and methods were used in determining PODs for the derivation of RfDs. EPA conducted benchmark dose modelling on the increased incidence of a constellation of lesions in the liver. Benchmark dose modeling was conducted consistent with EPA's *Benchmark Dose Technical Guidance*

Document to derive BMDLs (EPA, 2012). A BMR of 10% extra risk for dichotomous data (i.e., liver lesions) was chosen per EPA's *Benchmark Dose Technical Guidance* (EPA, 2012). This resulted in a $BMDL_{10}$ of 0.09 mg/kg-day as the POD. This POD is an external dose as opposed to the internal dose-based POD's derived for PFOA and PFOS (an internal dose was not derived). EPA estimated an HED (i.e., POD_{HED}) of 0.01 mg/kg-day (using a dosimetric adjustment factor [DAF]) and applied a composite UF of 3,000 to **derive a chronic RfD of 3E-06 mg/kg-day**. UFs were applied according to methods described in EPA's *Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002).

<u>Cancer Endpoint</u> – EPA concluded that there is *Suggestive Evidence of Carcinogenic Potential* from oral exposure to GenX chemicals in humans. This is based on a single cancer bioassay (a chronic 2-year study in rats) for HFPO-DA and its ammonium salt that showed increased incidence of liver tumors (female) and combined pancreatic acinar adenomas and carcinomas (males) in rats at high doses only. EPA determined that the existing evidence from this single chronic study is considered inadequate to justify a quantitative assessment. As a result, CSFs were not derived.

EPA Status. In April of this year, EPA finalized a National Primary Drinking Water Regulation (NPDWR) for six PFAS substances. Under the NPDWR, EPA established an MCL of 10 ng/L (or ppt) for HFPO-DA (GenX Chemicals). EPA set the MCLG for GenX at 10 ng/L based on protection of noncancer effects using the Office of Water chronic oral RfD of 3E-06 mg/kg-day. In addition, EPA set an MCL based on a hazard index of 1 for mixtures of two or more of the following PFAS: HFPO-DA, PFBS, PFHxS, and PFNA. That is, the sum of the concentrations for HFPO-DA, PFBS, PFHxS, and PFNA cannot exceed a hazard index of 1. Both MCLs (for carcinogens and noncarcinogens) and MCLGs (for noncarcinogens) are identified as ARARs under MTCA (*see* WAC 173-340-720(3)(b)). In May of this year, EPA updated its RSL tables. EPA's May 2024 RSLs for HFPO-DA have been calculated using the EPA Office of Water derived oral RfD of 3E-06 mg/kg-day.

Acronyms

µg/L	Microgram per liter
ADAF	Age-dependent adjustment factor
ARAR	Applicable or Relevant and Appropriate Requirements
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
BMDL	Benchmark Dose Lower Bound
BMR	Benchmark response
CLARC	Cleanup Levels and Risk Calculations (Ecology Database)
CSF	Cancer Slope Factor
DAF	Dosimetric Adjustment Factor
DOH	Washington State Department of Health
Ecology	Washington State Department of Ecology
EPA	Environmental Protection Agency
HED	Human Equivalent Dose
HFPO-DA	Hexafluoropropylene Oxide Dimer Acid
IRIS	Integrated Risk Information System
LOAEL	Lowest Observed Adverse Effect Level
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDH	Minnesota Department of Health
mg/kg-day	Milligram per kilogram per day
mg/L	Milligram per liter
MOA	Mutagenic mode of action
MRL	Minimal Risk Level
MTCA	Model Toxics Control Act
ng/L	Nanogram per liter. Same as part per trillion.
ng/mL	Nanogram per milliliter. Same as microgram per liter or part per billion.
NHDES	New Hampshire Department of Environmental Services
NOAEL	No Observed Adverse Effect Level
NPDWR	National Primary Drinking Water Regulation
NTP	National Toxicology Program
ORD	Office of Research and Development
PFAS	Per- and Polyfluoroalkyl Substances
PFBA	Perfluorobutanoic acid; Perfluorobutanoate
PFBS	Perfluorobutane sulfonic acid; Perfluorobutane sulfonate
PFHxA	Perfluorohexanoic acid; Perfluorohexanoate
PFHxS	Perfluorohexanesulfonic acid; Perfluorohexane sulfonate
PFNA	Perfluorononanoic acid; Perfluorononanoate
PFOA	Perfluorooctanoic acid; Perfluorooctanoate
PFOS	Perfluorooctane sulfonic acid; Perfluorooctane sulfonate
POD	Point of Departure
PPRTV	Provisional Peer-Reviewed Toxicity Value
ppt	Parts per trillion

RfD	Reference Dose
RSL	Regional Screening Level
SAB	Science Advisory Board
SAL	State Action Level
UF	Uncertainty Factor

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ATTACHMENT 1

STATE OF WASHINGTON
DEPARTMENT OF ECOLOGY
PO Box 47600 • Olympia, WA 98504-7600 • 360-407-6000
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Date: March 24, 2022

To: Andrea LaTier and Elizabeth Allen – EPA Region 10 Risk Evaluation Branch

From: Andy Kallus – Ecology Toxics Cleanup Program (TCP)

Subject: Adoption of Human Health Toxicity Criteria for PFAS Chemicals

Cc: Valerie Bound, Richelle Perez, and Mark Gordon – Ecology TCP

Purpose and Background: The purpose of this memo is to provide the United States Environmental Protection Agency (EPA) Region 10 with our approach and recommendations for selecting human health toxicity values for the following five per- and polyfluoroalkyl substances (PFAS): PFOA, PFOS, PFNA, PFHxS, and PFBS. All acronyms used in this memo are defined in a list at the end the text, and references cited are provided after the acronym list.

In October 2021, the Washington State Department of Ecology (Ecology) concluded that per- and polyfluoroalkyl substances (PFAS) are hazardous substances under the Model Toxics Control Act (MTCA) (October 21, 2021 Site Register[1]). Also, On January 1, 2022 the Washington Department of Health (DOH) issued final groundwater State Action Levels (SALs)[2] for the five PFAS compounds listed above. The SALs were derived using peer-reviewed non-cancer reference doses (RfDs) that represent the best and latest science. RfDs were used for establishing the SALs because data are limited at this time to support a quantitative assessment of cancer risk for PFAS compounds.

MTCA Hierarchy of Toxicological Data Sources: WAC Section 173-340-708 of the MTCA rule establishes a hierarchy of toxicological data sources. Under the rule, toxicity values published in EPA's Integrated Risk Information System (IRIS) shall be used when available to establish cleanup levels. If an IRIS value is not available, toxicity values published in EPA's Health Effects Assessment Summary Tables (HEAST), or where more appropriate, the National Center for Environmental Assessment (NCEA), shall be used. EPA's NCEA develops toxicity data in support of EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) program. NCEA

[1] https://apps.ecology.wa.gov/publications/documents/2109041u.pdf
[2] https://doh.wa.gov/community-and-environment/drinking-water/regulation-and-compliance/rule-making

is now known known as the Center for Public Health and Environmental Assessment (CPHEA), and is part of EPA's Office of Research and Development (ORD). EPA develops toxicity data from the PPRTV program in response to requests and needs of the Superfund Program.

EPA's HEAST, which was last updated in 1997, is considered to be a Tier 3 toxicity source according to EPA's 2003 Memorandum on *Human Health Toxicity Values in Superfund Risk Assessment* [3](EPA, 1997; EPA, 2003). Values in HEAST are archived when an IRIS or an EPA PPRTV is released. As such, Ecology has concluded that both IRIS and PPRTV toxicity values are more appropriate sources of toxicological information than values from HEAST.

Of the five PFAS chemicals evaluated by DOH for SAL development, only one (PFBS) has an available RfD from the MTCA sources listed above. For PFBS, DOH used EPA's 2021 chronic oral RfD PPRTV value[4] of 300 ng/kg-day for the development of their SAL (DOH, 2021; EPA, 2021). Per WAC 173-340-708(7), when a RfD is not available through the specified sources, Ecology shall establish one on a case by case basis and in consultation with other experts, including EPA.

It's noted that for two of the PFAS chemicals (PFOA and PFNA), DOH selected toxicity values developed by the Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 2021). According to EPA's 2003 hierarchy guidance for toxicity values, ATSDR minimal risk levels (MRLs) [5] may be a suitable Tier 3 source for toxicity data (EPA, 2003). The 2003 EPA guidance also states that ATSDR's toxicological profiles, which provide the basis for the MRLs, "are peer reviewed, are available to the public, and are transparent about the methods and processes used to develop the values" (EPA, 2003).

Selection of Human Health Toxicity Criteria for PFAS Chemicals: For the purpose of developing MTCA cleanup levels for the five PFAS chemicals listed above, Ecology believes that the oral RfDs selected by DOH in the development of their SALs, which includes EPA's 2021 PPRTV RfD for PFBS, are appropriate and represent the best and latest science. The toxicity studies that form the basis of the SALs are high quality, peer-reviewed, comprehensive, and based on current scientific research by U.S. federal and state governments (DOH, 2021). Also, the techniques used in the development of the RfDs are consistent with those recommended in MTCA in which the identified point of departure (POD; e.g., NOAEL, LOAEL, BMDL)[6] for the critical effect, as identified from studies on laboratory animals, is divided by various uncertainty factors (e.g., extrapolating animal data to human, database deficiencies) to derive the RfD (WAC 173-340-708(7)(f)).

PFOA, PFOS, PFNA, and PFHxS are readily absorbed from food and water, but only slowly eliminated from the human body (central tendency half-lives of 2.3 to 5.3 years). As such, the

[3] https://www.epa.gov/sites/default/files/2015-11/documents/hhmemo.pdf
[4] https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=350888
[5] MRLs are developed by ATSDR and can be used as an RfD. An MRL is an estimate of the amount of a chemical a person can eat, drink, or breathe each day without a detectable risk to health. MRLs are developed for noncancer endpoints (DOH, 2021).
[6] Point of Departure (POD): The NOAEL, LOAEL or BMDL that defines the minimal or no effect level in animals in the critical study, and marks the beginning of a low-dose extrapolation (e.g., animal data to human extrapolations). For PFBS, the POD is a dose in mg/kg-day. For the other PFAS, it is a serum level in mg/L.

critical study selected by DOH for these PFAS was limited to studies that measured internal dose (concentrations in serum) or had sufficient data to model serum level across the dose-range. For these PFAS, internal dose (serum level) rather than the external dose (administered dose) was used to represent the POD in animal studies (DOH, 2021).

A discussion of the selected toxicity criteria used in the development of the DOH SAL for each PFAS compound is provided below, and is summarized in **Table 1** (located at the end of the memo on Page 10). The toxicity criteria presented in **Table 1** will be used by Ecology to develop MTCA cleanup levels.

- **Perfluorooctanoic acid (PFOA)** – Toxicity data for PFOA is not available from any of toxicity sources identified in the MTCA Rule.

  EPA's current health advisory (HA) of 70 ng/L for PFOA was developed by EPA's Office of Water (Health and Ecological Criteria Division) and is based on a chronic RfD of 20 ng/kg-day (EPA, 2016a). EPA based its RfD on a developmental study using mice (published in 2006) that generated a LOAEL of 1 mg/kg-day and an estimated maternal serum level of 38 mg/L—based on developmental effects of gestational exposure in mice (Lau et al., 2006; EPA, 2016a). A NOAEL was not determined. EPA estimated a human equivalent dose (HED) of 5.3E-03 mg/kg-day[7] and applied a composite uncertainty factor (UF) of 300 to derive the RfD.

  ATSDR based its intermediate MRL of 3 ng/kg-day on a more recent developmental study using mice (published in 2016) that generated a LOAEL of 0.3 mg/kg-day and an estimated maternal serum level of 8.29 mg/L—based on developmental effects in mouse offspring in adulthood following gestational exposure (Koskela et al. 2016; ATSDR, 2021). A NOAEL was not determined. ATSDR estimated an HED 8.21E-04 mg/kg-day and, like EPA, applied a composite UF of 300 to derive the RfD.

  DOH Recommendation. DOH selected ATSDR's MRL of 3 ng/kg-day as the best basis for development of a SAL for PFOA (DOH, 2021). Both EPA's RfD and ATSDR's MRL are based on developmental effects in mice that were administered PFOA during gestation, and the studies are comparable in duration and applied the same composite UF. The Koskela et al. 2016 study encompassed a lower administered dose than the Lau et al. 2006 study, and this resulted in a lower value for the LOAEL.

  EPA Status. At this time, PFOA has not been identified for development of a toxicity assessment under EPA's IRIS program. However, EPA is moving forward with the process to develop a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for PFOA under the Safe Drinking Water Act (SDWA). The NPDWR sets a legally enforceable limit for PFOA called a Maximum Contaminant Level (MCL). The MCLG is set at a level at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety. As part of the development of an MCLG for PFOA, EPA is reviewing relevant toxicity data to derive an updated chronic RfD and, if appropriate data are

[7] The human equivalent dose (HED) is an estimated daily intake in humans that would produce the estimated maternal serum level at the POD (e.g., internal dose at the NOAEL, LOAEL) in a human population. Dosimetric adjustment factors (DAF) or pharmacokinetic modeling techniques are used to convert animal doses to HEDs. For PFBS, EPA applied a DAF to the external administered dose at the POD to derive the HED.

available, a cancer slope factor. Both MCLs and MCLGs are identified as Applicable or Relevant and Appropriate Requirements (ARARs) under MTCA (*see* WAC 173-340-720(3)(b)).

- **Perfluorooctane sulfonic acid (PFOS)** – Toxicity data for PFOS is not available from any of toxicity sources identified in the MTCA Rule.

  Like PFOA, EPA's current HA for PFOS is also 70 ng/L, is based on a chronic RfD of 20 ng/kg-day, and was developed by EPA's Office of Water (Health and Ecological Criteria Division) (EPA, 2016b). EPA based its RfD on a developmental study using rats (published in 2005) that generated a NOAEL of 0.1 mg/kg-day and an estimated maternal serum level of 6.26 mg/L—based on reduced pup weight and developmental delays in rats (Luebker et al., 2005; EPA, 2016b). EPA estimated an HED of 5.1E-04 mg/kg-day and applied a composite UF of 30 to derive the RfD.

  ATSDR also selected the NOAEL of 0.1 mg/kg-day from the Luebker et al., 2005 study to derive its intermediate MRL. However, they modeled a time-weighted average maternal serum level of 7.4 mg/L at the NOAEL (ATSDR, 2021). ATSDR estimated an HED of 5.15E-04 mg/kg-day (comparable to EPA's) and applied a composite UF of 300 (10 times EPA's UF) to derive the MRL. ATSDR applied the same individual UFs as EPA, but applied an additional ten-fold modifying factor to account for insufficient pharmacological data in critical studies for immunotoxicity. This resulted in the derivation of an intermediate MRL of 2 ng/kg-day.

  DOH Recommendation. DOH concurred with the Minnesota Department of Health (MDH, 2019a) and the New Hampshire Department of Environmental Services (NHDES, 2019) on their derivation of the chronic RfD for PFOS based on immune effects to adult male mice as reported in the Dong et al. 2011 study. DOH concluded that while rodents are sensitive to both immune and developmental effects of PFOS, reduced antibody response to an antigen (immune effects) appears to be a more sensitive endpoint (DOH, 2021). The Dong et al. 2011 study generated a NOAEL of 0.0167 mg/kg-day and an estimated serum level of 2.36 mg/L—based on immune effects in adult male mice (Dong et al., 2011). MDH estimated an HED of 3.07E-04 mg/kg-day (using a dosimetric adjustment factor [DAF]) and applied a composite UF of 100 to derive the RfD. This resulted in the derivation of a chronic RfD of 3 ng/kg-day.

  Some of the rationale for DOH's selection of the RfD developed by MDH and NHDES based on the Dong et al. 2011 study is provided below (DOH, 2021).

  - Reduced antibody response to an antigen (immune effects) appears to be a more sensitive endpoint than developmental effects.
  - While there are uncertainties in the toxicokinetics for the mouse strains used in the various immune studies, the critical study (Dong et al. 2011) measured PFOS levels in mouse serum at the end of the experiment.
  - The experiment was 60 days long and was supported by two other 60-day studies in the same strain of mouse with similar serum measurements indicating reproducibility.

- T-Cell-Dependent Antibody Response (TDAR) assays, like the one used in Dong et al. 2011, are validated, well regarded evidence of immune suppression and are relevant to humans.
- Both immune and developmental endpoints have supporting epidemiological data to indicate their relevance for humans. In adults and children, PFOS exposure has been associated with suppressed antibody response to vaccines in a number of studies in different populations.

EPA Status. At this time, PFOS has not been identified for development of a toxicity assessment under EPA's IRIS program. However, EPA is moving forward with the process to develop an MCLG and NPDWR for PFOS under the SDWA (*see* prior discussion for PFOA under EPA Status).

- **Perfluorononanoic acid (PFNA)** – Toxicity data for PFNA is not available from any of toxicity sources identified in the MTCA Rule. DOH reviewed toxicity assessments that included a target serum level derived by the New Jersey Drinking Water Quality Institute (NJ DWQI), an MRL derived by ATSDR, and RfDs developed NHDES and the Michigan Science Advisory Workgroup (MSWG).

  DOH Recommendation. DOH selected the ATSDR intermediate MRL for development of the SAL. ATSDR based its intermediate MRL of 3 ng/kg-day on a developmental study using bred female mice (published in 2015) that generated a NOAEL of 1 mg/kg-day and an estimated maternal serum level of 6.8 mg/L—based on reduced growth and delayed development in pups exposed prenatally (Das et al. 2015; ATSDR, 2021). ATSDR estimated an HED of 1.0E-03 mg/kg-day (using a DAF) and applied a composite UF of 300 to derive the RfD. It's noted that the MSWG also used the Das et al. 2015 study to derive its chronic RfD (MSWG, 2019; Das et al. 2015). However, MSWG derived a lower HED by applying a serum half-life of 3.9 years (from Zhang et al. 2013) in ATSDR's DAF calculation. This resulted in a chronic RfD of 2.2 ng/kg-day.

  Like MSWG, DOH modified the MRL slightly by incorporating an updated elimination serum half-life based on a recent three-year biomonitoring study in a New Jersey community exposed to elevated PFNA in their drinking water (Yu et al., 2021). Based on the Yu et al. study, DOH applied a serum half-life of 3.52 years (ATSDR used 2.5 years; MSWG used 3.9 years) in ATSDR's DAF calculation to derive an HED of 7.34E-04 mg/kg-day. This resulted in a modified MRL of 2.5 ng/kg-day.

  EPA Status. EPA has not developed toxicity criteria for PFNA and has not established a screening level in tap water. A toxicity assessment is currently under draft development (Step 1) for PFNA by EPA's IRIS Program.

- **Perfluorohexanesulfonic acid (PFHxS)** – Toxicity data for PFHxS is not available from any of toxicity sources identified in the MTCA Rule. DOH reviewed toxicity assessments that included an MRL derived by ATSDR, an RfD developed NHDES, and RfDs developed by MDH and MSWG.

  ATSDR based its intermediate MRL of 20 ng/kg-day on a reproductive and developmental study using rats (published in 2009) that generated a NOAEL of 1 mg/kg-day and an estimated serum level of 73.2 mg/L—based on thyroid effects in adult male rats (Butenhoff et al. 2009; ATSDR, 2021). ATSDR estimated an HED 4.7E-03 mg/kg-day and applied a composite UF of 300 to derive the RfD.

DOH Recommendation. Since the ATSDR MRL was first derived (in 2018), new high-quality studies on PFHxS have become available (DOH, 2021). Rather than use the ATSDR MRL, DOH selected the MDH chronic RfD of 9.7 ng/kg-day for the development of their SAL (DOH, 2021; MDH, 2019b). The critical study behind the MDH RfD is a 28-day oral gavage study on adult male and female rats conducted by the National Toxicology Program (NTP) (NTP, 2019). MDH conducted benchmark dose modeling of the total and free T4 (thyroxine) data in males and females in the NTP study (MDH, 2019b). MDH selected a benchmark dose lower-confidence limit for 20 percent reduction in thyroxine (free T4) in male rats ($BMDL_{20\%}$)[8] as the POD. The estimated serum level at $BMDL_{20\%}$ was 32.4 mg/L. MDH estimated an HED of 2.92E-03 mg/kg-day (using a DAF) and applied a composite UF of 300 to derive the RfD.

EPA Status. EPA has not developed toxicity criteria for PFHxS and has not established a screening level in tap water. A toxicity assessment is currently under draft development (Step 1) for PFHxS by EPA's IRIS Program.

- **Perfluorobutane sulfonic acid (PFBS)** – DOH selected EPA's 2021 chronic oral RfD PPRTV value of 300 ng/kg-day for the development of their SAL for PFBS (DOH, 2021; EPA, 2021). EPA PPRTV toxicity values are included in MTCA's hierarchy of toxicity sources.

  The critical study behind the EPA PPRTV RfD is a study (published in 2017) that evaluated the influence of prenatal (before birth) PFBS exposure on perinatal (before and after birth) growth and development, pubertal onset, and reproductive and thyroid endocrine system in female mice (Feng, 2017). EPA conducted benchmark dose modeling of the total T4 (thyroxine) data in newborn female offspring of mice in the Feng et al. 2017 study (Feng et al., 2017). EPA selected a benchmark dose lower-confidence limit for a total T4 reduction of one half the standard deviation compared to controls in newborn female offspring ($BMDL_{0.5\ SD}$) as the POD. This resulted in an external dose of 22.1 mg/kg-day as the POD (an internal dose was not derived). EPA estimated an HED of 0.095 mg/kg-day (using a DAF) and applied a composite UF of 300 to derive the RfD.

  EPA Status. PFBS is listed in EPA's Regional Screening Level (RSL) table with an oral RfD of 300 ng/kg-day (PPRTV toxicity value) and a tap water screening value of 6 ug/L (based on a hazard quotient of 1). At this time, PFBS has not been identified for development of a toxicity assessment under EPA's IRIS program.

[8] BMDL is the lower limit of the 95 percent confidence interval on the benchmark dose.

Acronyms

ARAR	Applicable or Relevant and Appropriate Requirements
ATSDR	Agency for Toxic Substances and Disease Registry
BMDL	Benchmark Dose Lower Bound
CPHEA	Center for Public Health and Environmental Assessment
DAF	Dosimetric Adjustment Factor
DOH	Washington State Department of Health
Ecology	Washington State Department of Ecology
EPA	Environmental Protection Agency
HA	Health Advisory
HEAST	Health Effects Assessment Summary Tables
HED	Human Equivalent Dose
IRIS	Integrated Risk Information System
LOAEL	Lowest Observed Adverse Effect Level
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDH	Minnesota Department of Health
MRL	Minimal Risk Level
MSWG	Michigan Science Advisory Workgroup
MTCA	Model Toxics Control Act
NCEA	National Center for Environmental Assessment
NHDES	New Hampshire Department of Environmental Services
NJ DWQI	New Jersey Drinking Water Quality Institute
NOAEL	No Observed Adverse Effect Level
NPDWR	National Primary Drinking Water Regulation
NTP	National Toxicology Program
ORD	Office of Research and Development
PFAS	Per- and Polyfluoroalkyl Substances
PFBS	Perfluorobutane sulfonic acid; Perfluorobutane sulfonate
PFHxS	Perfluorohexanesulfonic acid; Perfluorohexane sulfonate
PFNA	Perfluorononanoic acid; Perfluorononanoate
PFOA	Perfluorooctanoic acid; Perfluorooctanoate
PFOS	Perfluorooctane sulfonic acid; Perfluorooctane sulfonate
POD	Point of Departure
PPRTV	Provisional Peer-Reviewed Toxicity Value
RfD	Reference Dose
SAL	State Action Level
SDWA	Safe Drinking Water Act
TDAR	T-Cell-Dependent Antibody Response
UF	Uncertainty Factor
WAC	Washington Administrative Code

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Table 1. Summary of Noncancer Toxicity Criteria Selected by DOH for the Development of SALs

PFAS	Critical Effect	Serum Level at Critical Effect (Internal Dose)[1]	Human Equivalent Dose[2]	Composite UF[3]	RfD or MRL[4]
PFOA	**ATSDR, 2021**. LOAEL (0.3 mg/kg-d) for skeletal effects in mouse offspring in adulthood following gestational exposure.	8.29 mg/L	0.000821 mg/kg-d	300	**Intermediate MRL** 0.000821 mg/kg-d ÷ 300 = **3 ng/kg-d**
PFOS	**MDH 2019a/NHDES 2019.** NOAEL (0.0167 mg/kg-d) for immune effects in adult male mice.	2.36 mg/L	0.000307 mg/kg-d	100	**Chronic RfD** 0.000307 mg/kg-d ÷ 100 = **3 ng/kg-d**
PFNA	**ATSDR, 2021**. NOAEL (1 mg/kg-d) for reduced pup weight and developmental delays in mice.	6.8 mg/L	0.000734 mg/kg-d[5]	300	**Intermediate MRL (modified)[5]** 0.000734 mg/kg-d ÷ 300 = **2.5 ng/kg-d**
PFHxS	**MDH 2019b.** $BMDL_{20\%}$ for reduced thyroxine (free T4) in adult male rats (i.e., 20% reduction in thyroxine [free T4] in adult male rats).	32.4 mg/L	0.00292 mg/kg-d	300	**Chronic RfD** 0.00292 mg/kg-d ÷ 300 = **9.7 ng/kg-d**
PFBS	**EPA, 2021.** $BMDL_{0.5\ \text{Std Dev (SD)}}$ of 22.1 mg/kg-d for reduced thyroid hormone (total T4) in newborn female offspring of mice dosed during pregnancy (i.e., decline of one half the standard deviation in thyroxine [total T4] in newborn female offspring of mice).	not estimated	0.095 mg/kg-d	300	**Chronic RfD** 0.095 mg/kg-d ÷ 300 = **300 ng/kg-d**

Notes:

[1] Predicted or measured serum level in the laboratory test animal (internal dose) from the critical study at the point of departure.

[2] The internal dose (where available) was used as the basis for extrapolations of the dose-response points of departure from animal studies to human equivalent doses.

[3] UF = Uncertainty Factor. One of several, generally 10-fold, default factors used in deriving the RfD from experimental data.

[4] RfD = Oral Reference Dose. ATSDR uses the term minimal risk level or MRL rather than RfD.

[5] For PFNA, DOH applied a serum half-life of 3.52 years in ATSDR's dosimetric adjustment factor (DAF) calculation to derive a human equivalent dose of 0.000734 mg/kg-day. The updated half-life is based on a three-year biomonitoring study in a New Jersey community exposed to elevated PFNA in their drinking water (Yu et al., 2021). ATSDR applied a serum half-life of 2.5 years in the DAF calculation that yielded a human equivalent dose of 0.001 mg/kg-day