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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

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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 adopting 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.** $BMDL_{0.5\ Std\ Dev\ (SD)}$ 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