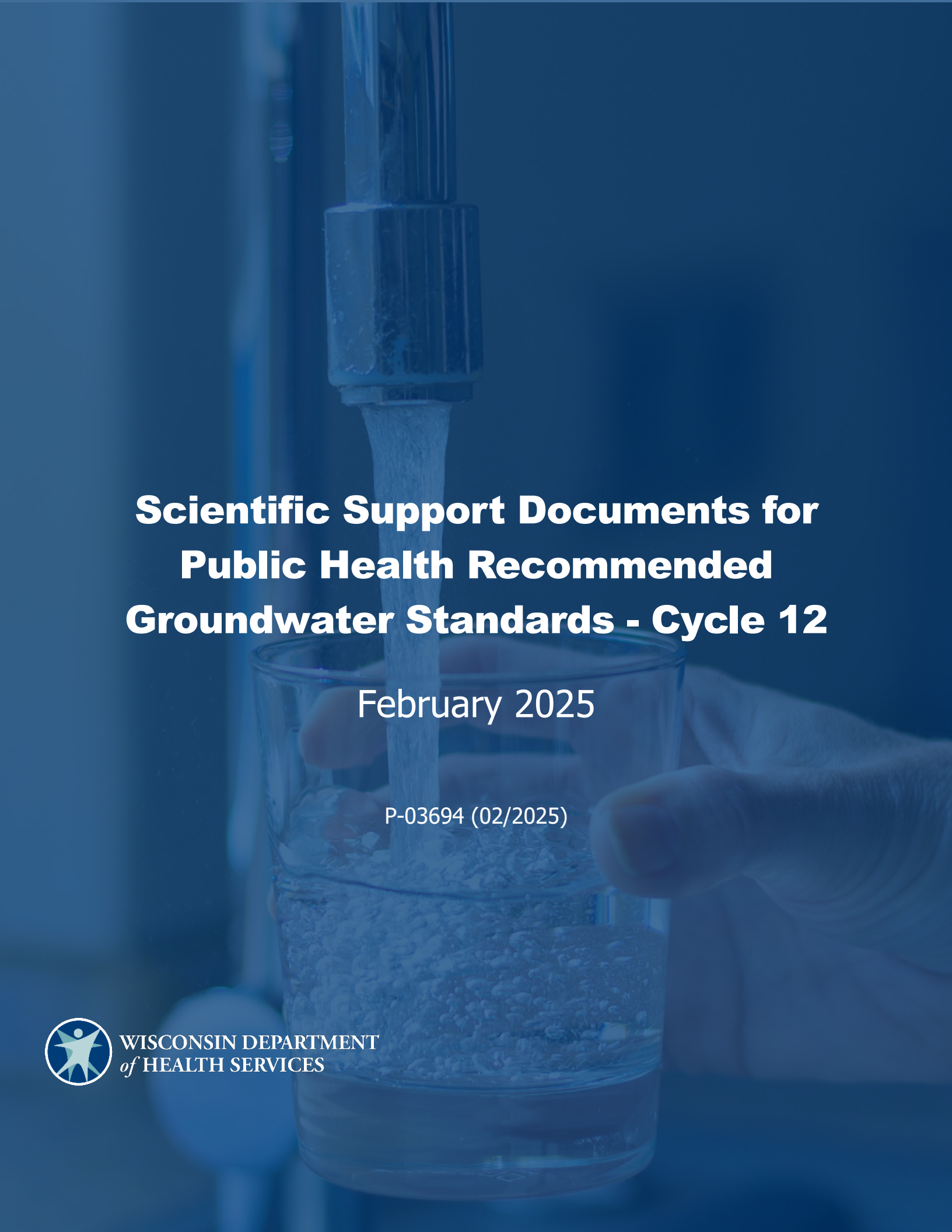

Scientific Support Documents for Public Health Recommended Groundwater Standards - Cycle 12

February 2025

P-03694 (02/2025)

WISCONSIN DEPARTMENT *of* HEALTH SERVICES

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*Also referred to as GenX™

PFOA | 2024

Substance Overview

Perfluorooctanoic acid (PFOA) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS).[1-3] PFOA is made up of eight carbon-fluorine bonds and a carboxylic acid group.[1-3] Because PFOA contains eight carbon-fluorine bonds, it is considered a long-chain PFAS.[1-3] Long-chain PFAS, like PFOA, stay in the human body for a long time.[1, 3]

Historically, PFOA was used as an emulsifier and surfactant in a number of industrial and commercial products, such as fluoropolymers, aqueous fire-fighting foams, cosmetics, lubricants, and paints.[1-3] In 2006, eight major chemical manufacturers agreed to phase out the use of PFOA and PFOA-related chemicals in their products and related emissions from their facilities by 2015 as part of the PFOA Stewardship Program.[2, 4] However, because this program was voluntary, PFOA may still be present in imported products or formed as by-products in the manufacturing of other products.[2]

Recommendations

Recommended Standards	
Enforcement Standard:	4 ng/L
Preventive Action Limit:	0.4 ng/L

The Wisconsin Department of Health Services (DHS) recommends an enforcement standard of four nanograms per liter (ng/L) for PFOA. The recommended standard is based on the maximum contaminant level (MCL) that the United State Environmental Protection Agency (EPA) established for PFOA in 2024. DHS recommends that the preventive action limit for PFOA be set at 10% of the enforcement standard because PFOA has been shown to cause carcinogenic, mutagenic, teratogenic, and interactive effects.

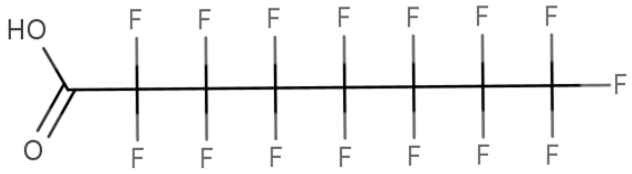
Health Effects

Studies among people and in research animals indicate the PFOA exposure can damage the liver, impact the immune and cardiovascular systems, and affect development.[1, 3]

Exposure Routes

People can be exposed to PFOA by drinking contaminated water, swallowing contaminated soil, eating food that was packaged in material that contains PFOA, consuming fish from contaminated waters, and breathing in or swallowing dust that contains PFOA.[1-3] Additionally, babies born to mothers exposed to PFOA can be exposed to PFOA during pregnancy and breastfeeding.[1-3]

Chemical Profile

PFOA	
Structure:	
CAS Number:	335-67-1
Formula:	$C_8HF_{15}O_2$
Molar Mass:	414.07 g/mol
Synonyms:	Pentadecafluorooctanoic acid Perfluoro-n-octanoic acid Perfluoroheptanecarboxylic acid Pentadecafluoro-1-octanoic acid Pentadecafluoro-n-octanoic acid n-perfluorooctanoic acid Perfluorooctylcarboxylic acid Perfluorocaprylic acid 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctanoic acid

This information was obtained from the PubChem database.[5]

Current Standard

Wisconsin does not currently have NR140 Groundwater Quality Public Health Standards for PFOA.[6]

In 2020, DHS recommended a combined enforcement standard of 20 nanograms per liter (ng/L) for perfluorooctane sulfonate (PFOS), n-ethyl perfluorooctane sulfonamideoethanol (NEtFOSE), n-ethyl perfluorooctane sulfonamidacetic acid, (NEtFOSAA), n-ethyl perfluorooctane sulfonamide (NEtFOSA), and perfluorooctane sulfonamide (FOSA).

Our recommended standard was based on a modeling approach that estimated how much PFOA a mother had to be exposed to to protect the baby from developmental effects. We recommended a combined standard because studies have shown that PFOA and PFOS can cause similar effects in humans and in animals and because NEtFOSE, NEtFOSAA, NEtFOSA, and FOSA breakdown into PFOS in the body and the environment. We recommended a preventive action limit of 2 ng/L – 10% of the enforcement standard – due to carcinogenic, mutagenic, and interactive effects.

These standards, however, were not adopted in rule.[7,a]

a In August 2022, the DNR started a rule-making effort to establish groundwater standards for PFOA, PFOS, PFBS, and HFPO-DA based on DHS' recommendations. In December 2023, this rule package was sent to the state legislature because the estimated economic impact of the proposed changes was more than 20 million dollars, which requires the legislature to approve further action. No additional action on this rule package has been made as of September 2024.

Standard Development

The process for developing groundwater standards is specified in Wis. Stat. ch. 160.[8] To develop recommended public health groundwater standards, we (DHS) gather relevant scientific information, select the appropriate standard based on statutory requirements, and document these findings.

Available Scientific Information for PFOA	
Federal Numbers	
Maximum Contaminant Level (Individual):	**Yes**
Maximum Contaminant Level (Hazard Index):	No
Health Advisory:	No
Drinking Water Concentration (Cancer Risk):	No
State Drinking Water Standard	
NR 809 Maximum Contaminant Level:	**Yes**
Acceptable Daily Intake	
EPA Human Health Toxicity Value:	**Yes**
Oncogenic Potential	
EPA Cancer Slope Factor:	**Yes**
Guidance Values	
ATSDR Chronic Oral Minimum Risk Level:	**Yes**
Technical Information:	
Critical toxicology/epidemiology studies?	No

Federal Numbers

Wis. Stat. ch. 160, requires that DHS use the most recent federal number as the recommended enforcement standard.[8] This requirement does not apply if a federal number does not exist or there is significant technical information that was not considered when the federal number was established and this information indicates a different number should be used to set the standard.

Maximum Contaminant Level

In April 2024, the United States Environmental Protection Agency (EPA) established a maximum contaminant level (MCL) of 4 nanograms per liter (ng/L) for PFOA.[9, 10]

The MCL is the highest level of a substance that is allowed in drinking water served by public water systems as defined by the Safe Drinking Water Act.[11] To establish an MCL, the EPA first establishes a maximum contaminant level goal (MCLG) – the level of a substance at which health effects are not expected to occur while allowing for an adequate margin of safety.[12] For substances classified as either "carcinogenic to humans" or "likely to be carcinogenic to humans," EPA sets the MCLG at zero because there is no known safe level of exposure for these substances.[10,b]

b For these substances, EPA follows the linear default extrapolation approach in establishing the MCLG.[9] This approach assumes that there is a proportional relationship between dose and carcinogenicity at low concentrations that extrapolate to zero. This approach ensures that the MCLG is set at a level where there are no known or anticipated adverse health effects – zero.

For substances with an MCLG of zero, the EPA sets the Maximum Contaminant Level (MCL) as close to the MCLG as feasible. In these cases, EPA typically sets the MCL at the practical quantitation limit (PQL).

For PFOA, EPA determined that the PQL is 4 ng/L.[10] As such, the EPA set the MCL for PFOA equal to the PQL of 4 ng/L.

Health Advisory

EPA does not currently have a drinking water health advisory for PFOA.[13,c]

Drinking Water Concentration (Cancer Risk)

EPA does not have drinking water concentrations based on cancer risk for PFOA.

State Drinking Water Standard

Wis. Stat. ch. 160, requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

In 2020, Wisconsin adopted a maximum contaminant level of 70 nanograms per liter for PFOA and PFOS.[14] This standard is based on EPA's 2016 lifetime health advisory.[15]

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, sometimes termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Information System (IRIS) program.

EPA Oral Reference Dose

In 2023, EPA's Office of Research and Development established an oral reference dose of 3×10^{-8} milligrams PFOA per kilogram bodyweight per day (mg/kg-d).[3, 16]

The EPA identified three critical studies that observed associations between PFOA exposure and decreased serum anti-tetanus and anti-diphtheria antibody concentrations among children, increased total cholesterol among adults, and decreased infant birth weight (**Figure A-1**).[17-19] For each study, EPA used benchmark dose modeling to obtain an internal point of departure (POD) from serum levels (**Table 1**). EPA then used a physiologically based pharmacokinetic (PBPK) model to convert the internal POD to a human-equivalent dose POD, which is the external exposure amount that it would take to result in the

c While EPA issued an interim drinking water health advisory for PFOA in 2022, they state that the advisories for PFOA and PFOS "no longer reflect the best available scientific information because they were based on draft noncancer toxicity values from the 2021 SAB review drafts of the PFOA and PFOS toxicity assessments."[12]

internal dose associated with indicated health outcome.[d] EPA then obtained the oral reference dose by dividing the human equivalent PODs by a total uncertainty factor.

Table 1. Endpoints, Points of Departure, and Uncertainty Factors used by EPA to establish the Oral Reference Dose for PFOA*

Reference	Outcome	Endpoint	$POD_{Internal}$ (ng/mL)	POD_{HED}	Uncertainty Factors	Reference Dose
Budtz-Jorgensen, 2018[17]	Decreased anti-tetanus antibody concentrations	$BMDL_{0.5SD}$	3.47	3.05×10^{-7} mg/kg-d	Interspecies: 1 Intraspecies: 10 Endpoint: 1 Duration: 1 Database: 1 Total: 10	3×10^{-8} mg/kg-d
Budtz-Jorgensen, 2018[17]	Decreased anti-diphtheria antibody concentrations	$BMDL_{0.5SD}$	3.32	2.92×10^{-7} mg/kg-d	Interspecies: 1 Intraspecies: 10 Endpoint: 1 Duration: 1 Database: 1 Total: 10	3×10^{-8} mg/kg-d
Dong et al., 2019[18]	Increased total cholesterol	$BMDL_{5RD}$	2.29	2.75×10^{-7} mg/kg-d	Interspecies: 1 Intraspecies: 10 Endpoint: 1 Duration: 1 Database: 1 Total: 10	3×10^{-8} mg/kg-d
Wikström et al., 2020[19]	Decreased birth weight	$BMDL_{5RD}$	2.2	2.92×10^{-7}	Interspecies: 1 Intraspecies: 10 Endpoint: 1 Duration: 1 Database: 1 Total: 10	3×10^{-8}

$BMDL_{0.5SD}$ = Lower bound dose corresponding to the 95% lower confidence limit for a change in the mean response equal to 0.5 SD from the control mean; $BMDL_{0.5SD}$ = Lower bound dose corresponding to the 95% lower confidence limit for a 5% change in response

*Adapted from Tables 4-8, 4-9, and 4.11 in EPA's *Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Salts*.[3]

d EPA selected the one-compartment human developmental model published by Verner et al. (2016). Details of this model and the adaptations that EPA made are provided in Section 4.1.3 of EPA's *Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Related Salts* Document.[3]

Oncogenic Potential

Wis. Stat. ch. 160, requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that a substance is carcinogenic and there is no federal number or ADI from the EPA, then we must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of a substance, we looked to see if the EPA, IARC, or another agency has classified the cancer potential of for that substance. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

As part of their toxicity review, the EPA classified PFOA as *"*likely to be carcinogenic to humans" based on the evidence of kidney and testicular cancer in humans and the increased incidence of tumors and cancers in research animals.[3, 15]

The IARC has classified PFOA as carcinogenic to humans (Group 1). They based this classification on data from studies in research animals and "strong mechanistic evidence that PFOA exhibits key characteristics of carcinogens in exposed humans."[20, 21]

EPA Cancer Slope Factor

As part of their toxicity review, the EPA established a cancer slope factor of 0.0293 $(mg/kg\text{-}d)^{-1}$ in 2024.[3] They established this value from an epidemiological study by Shearer et al. that found that PFOA exposure was associated with increased risk of renal cell carcinoma in adults in a dose-dependent manner.[22]

Additional Technical Information

Wis. Stat. ch. 160, allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PFOA, we searched for any guidance values that had been published since DHS completed the literature review for PFOA in April 2019 as part of the Cycle 10 Groundwater Standards request. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Reference Level

In 2021, the ATSDR released their final Toxicological Profile for Perfluoroalkyls.[1] In this Profile, they established an intermediate oral minimum risk level of 3 x 10^{-6} mg/kg-d for PFOA.[e]

ATSDR selected a developmental study by Koskela et al. as the critical study.[23] In this study, female mice were exposed to PFOA during pregnancy and offspring had impaired neurological development and skeletal alterations. The ATSDR identified a LOAEL of 0.3 mg/kg-d and then used a PBPK model to estimate a human equivalent dose of 0.000821 mg/kg-d.[f]

To obtain the intermediate oral minimum risk level, ATSDR applied a total uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (3), and using a LOAEL instead of a NOAEL (10).

Literature Search

To ensure that Wisconsin's public health groundwater standards are established based on the best available information, DHS searches for relevant health studies published after the last literature review completed for a health value from the EPA.[g] We used the Web of Science and PubMed databases to look for studies that related to toxicity, effects on a disease state, and the key health effects of genotoxicity, carcinogenicity, teratogenicity, and interactivity for use in establishing the appropriate preventive action limit.

We excluded studies that did not meet the Population, Exposure, Comparator, and Outcome (PECO) criteria described in **Table A-1**. After applying these exclusion criteria, we located five key toxicity studies (**Table A-2**) and 73 key epidemiological studies (**Supplemental Table**).

Critical Toxicology Studies

To be considered a critical toxicity study, the study must have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have the appropriate toxicity and pharmacokinetic information necessary to establish an ADI (i.e., identifiable toxicity value, measured serum concentrations, reported half-life).

None of the key toxicity studies meet the critical toxicity study criteria (**Table A-2**).

Critical Epidemiological Studies

To be considered a critical epidemiology paper, the study must contain dose-response data in a format that can be used to establish an acceptable daily intake (i.e., established benchmark dose level) or the

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e The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not establish a chronic oral MRL for PFOA because they did not identify chronic duration studies and their policy is to not extrapolate across exposure durations.

f ATSDR used a PBPK model published by Wambaugh et al. in 2013 to convert the level of PFOA in animal serum to a level in serum that would cause the same effect in humans. Details of the model and the parameters that ATSDR used in their analysis are provided in Appendix A of the *Toxicological Profile for Perfluoroalkyls*.

g The last literature search completed by EPA was in February 2023 by the Integrated Risk Information System program in their work to establish a draft oral refence dose for PFOA.

study must evaluate the impact of exposure at various concentrations of the substance in drinking water.

None of these studies met these criteria (**Supplemental Table**).

Key Health Studies

Wis. Stat. ch. 160, states that DHS must recommend a preventive action limit of 10% of the enforcement standard for substances that have carcinogenic, mutagenic, teratogenic, or interactive effects.[8]

Key Health Effects for Establishing the Preventive Action Limit	
Carcinogenic:	Evidence indicates that the substance can produce or incite cancer.
Mutagenic:	Evidence indicates that the substance can alter or damage DNA.
Teratogenic:	Evidence indicates that the substance can cause structural defects in unborn babies.
Interactive:	Evidence indicates that the substance can increase the toxicity of other substances or that the substance's toxicity can be increased by the presence of other substances.

To recommend the appropriate preventive action limit, we reviewed the available scientific information for evidence of the ability for PFOA to cause these key health effects.

Carcinogenicity

As noted above, the EPA and IARC have classified PFOA as likely to be carcinogenic to humans. This classification is based on data from epidemiological studies among people and toxicity studies in research animals.[3, 20, 21]

Mutagenicity

In their toxicology review, EPA found that the potential for PFOA to cause mutagenic effects were mixed – based on the available studies. Of note was a study by Franken et al. that found that PFOA exposure in adolescents was associated with increased DNA damage in peripheral blood cells and a study by Governini et al. that observed a significant increase in the DNA fragmentation of sperm in individuals with measurable levels of PFOA.[24, 25] In our literature review, we found another study indicating that PFOA can cause DNA damage to human sperm.[26]

Teratogenicity

In their toxicology review, EPA identified two studies that reported teratogenic effects in research animals. Lau et al. found that PFOA caused a statistically significant increase in the incidence of limb and tail defects and microcardia (small heart) in the offspring of mice exposed to PFOA during pregnancy.[27] In a similarly designed experiment, Yahia et al. observed an increased incidence of cleft sternum.[24] We did not find any additional studies on teratogenic effects in our literature search.

Interactivity

In their toxicology review, EPA identified that co-exposure to mixtures of PFAS, including PFOA, can produces dose-additive effects.[3, 16] They also found that many PFAS, including PFOA, cause health effects through the same processes – for instance by affecting thyroid hormone signaling or impacting immune

and liver function.[3, 16] In our literature search, we found numerous epidemiological studies that observed similar effects with PFAS mixtures containing PFOA.[28-41]

Standard Selection

DHS recommends an enforcement standard of 4 ng/L for PFOA.

State statute requires that DHS recommend a federal number (such as a maximum contaminant level, health advisory, drinking water concentration based on cancer risk) if one is available and there is no significant technical information to indicate that a different value is more appropriate.

Basis for Enforcement Standard

- ☒ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

The EPA's maximum contaminant level (MCL) for PFOA was established in April 2024 with their last scientific review completed in February 2023. In our review of toxicological and epidemiological information published since this time, we did not identify significant findings indicating that a value other than the MCL should be used to establish the enforcement standard.

DHS recommends a preventive action limit of 0.4 ng/L for PFOA.

DHS recommends that the preventive action limit for PFOA be set at 10% of the enforcement standard because studies have shown that PFOA can cause carcinogenic, mutagenic, teratogenic, and interactive effects.

Prepared by Sarah Yang, PhD with assistance from Becky Bowen, MPH, MS

Wisconsin Department of Health Services

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Appendix A: Literature Review Details

Table A-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria for PFBS Study Evaluation

Element	Toxicological Inclusion Criteria	Epidemiological Inclusion Criteria
Population:	Non-human mammalian animal species (whole organism) of any life-stage (including preconception, in utero, lactation, peripubertal, and adult stages).	Any population and life-stage (occupational or general population, including children and other sensitive populations).
Exposure:	Any exposure to PFOA only via oral routes for at least 28 days*	Any exposure to PFOA via oral routes.
Comparator:	A concurrent control group exposed to vehicle-only treatment or untreated control.	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of PFOA or exposure to PFOA for shorter periods of time.
Outcome:	All health outcomes	All health outcomes.

*Exceptions are studies that are conducted during reproduction and/or development.

This literature search was conducted in the National Institutes of Health's *PubMed* resource and Clarivate Analytics' *Web of Science* resource. We used the following search terms in the literature review:

Title/abstract: PFOA or "perfluorooctanoic acid" and the synonyms listed in Chemical Properties table
Subject area: toxicology, public environmental occupational health (Web of Science)
MeOH search terms: toxicology, epidemiology, public health (PubMed)
Language: English

Table A-2. PFOA Key/Critical Toxicity Studies

Reference	Exposure	Key Findings	Critical Toxicity Criteria	Relevant Toxicity Data	Uncertainty Factors	Candidate ADI
Zhang et al., 2023[42]	Male rats were exposed to 0, 1.25, 5 and 20 mg/kg-d PFOA through gavage for 28 days.	PFOA significantly increased relative liver weight in a dose-dependent manner. Highest dose of PFOA significantly increased glycogen level. Serum markers of liver function injury and lipid metabolism significantly impacted by PFOA exposure.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 1.25 mg/kg=d POD_{HED}: N/A	N/A	N/A
Meng et al., 2024[43]	Mice were exposed to 0, 0.2, 2 mg/L of PFOA through drinking water for 180 days.	PFOA caused inflammatory bowel disease-like damage to the mouse colon and damage to the intestinal barrier.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 0.2 mg/L POD_{HED}: N/A	N/A	N/A
Jung et al., 2024[44]	Pregnant mice were exposed to 0, 0.43, 1.7, and 6.8 mg/kg, PFOA by oral gavage for six-days a week for six months.	The survival rate of pups and the sex ratio of surviving mice decreased significantly at the highest dose. All doses increased relative liver weight in male and females.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 0.43 mg/kg POD_{HED}: N/A	N/A	N/A
Li et al., 2024[45]	Male rats were exposed to 0, 1, 5, and 15 mg/kg-d PFOA for up to 28 days via gavage.	All PFOA doses significantly increased relative liver weights and caused hepatocellular hypertrophy after 14 and 28 days. PFOA exposure also increased ACO and PROD activity after 14 and 28 days.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 1 mg/kg-d POD_{HED}: N/A	N/A	N/A

Reference	Exposure	Key Findings	Critical Toxicity Criteria	Relevant Toxicity Data	Uncertainty Factors	Candidate ADI
Perez-Gomez, et al., 2024[46]	Newborn mice were exposed one of the following treatments: - Filtered water + no infection - PFOA + no injection - Filtered water + PBS-injection - PFOA + PBS-injection - Filtered Water + TMEV-injection - PFOA + TMEV-injection PFOA exposure = 70 ppt in water	Prior to infection, PFOA-exposed mice had an imbalance between Th1, Th2, and Treg cytokines caused a suppression of IL-4 and IL-13 production. The PFOA + TMEV group experienced an increase in seizure frequency and severity.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ☒ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 70 ppt POD_{HED}: N/A	N/A	N/A

ACO: Peroxisomal Acyl-CoA oxidase (ACO) activity – a measure of peroxisome proliferation and peroxisomal enzymatic activities.
PROD: Pentoxyresorufin-O-dealkylase – a measure of microsomal enzymatic activity indicating constitutive androstane receptor (CAR) activation in the liver.
PBS: phosphate buffer solution
TMEV: Theiler's murine encephalomyelitis virus - naturally occurring murine virus used to model human neurological symptoms associated with viral infections

Figure A-1. EPA's Process for Selecting the Final Oral Reference Dose for PFOA

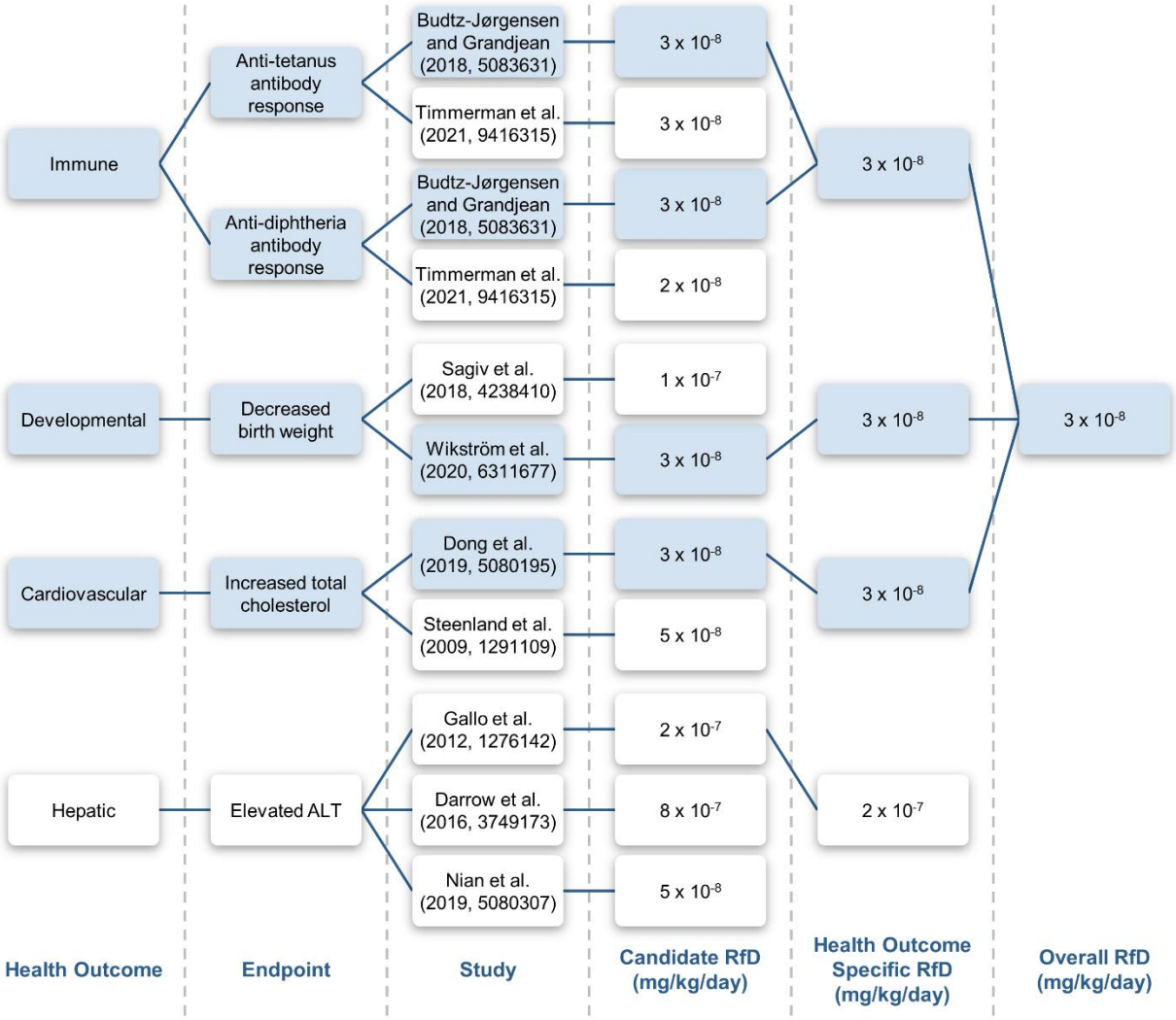

Figure 4-4 in EPA's *Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Related Salts*[3]

PFOS | 2024

Substance Overview

Perfluorooctanoic acid (PFOS) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS).[1-3] PFOS is made up of eight carbon-fluorine bonds and a sulfonic acid group. Because PFOS contains eight carbon-fluorine bonds, it is considered a long-chain PFAS. Long-chain PFAS, like PFOS, stay in the human body for a long time.[1-3]

Historically, PFOS was used as an emulsifier and surfactant in a number of industrial and commercial products, such as fluoropolymers, aqueous fire-fighting foams, cosmetics, lubricants, and paints.[1-3] The sole manufacturer of PFOS in the United States agreed to a voluntary phaseout in 2000, and the last reported production was in 2002. However, there are still some limited ongoing uses of PFOS and its precursors – like as a component of a certain photoresist substances and in some anti-reflective coatings.[2]

Recommendations

DHS recommends a Public Health Enforcement Standard of four nanograms per liter (ng/L) for PFOS. The recommended standard is based on the maximum contaminant level (MCL) that the United States Environmental Protection Agency (EPA) established for PFOS in 2024. DHS recommends that the Public Health Preventive Action Limit for PFOS be set at 10% of the enforcement standard because PFOS has been shown to cause carcinogenic, mutagenic, teratogenic, and interactive effects.

Recommended Standards	
Enforcement Standard:	4 ng/L
Preventive Action Limit:	0.4 ng/L

Health Effects

Studies among people and in research animals indicate the PFOS exposure can damage the liver, impact the immune and cardiovascular systems, and affect development.[1-3]

Exposure Routes

People can be exposed to PFOS by drinking contaminated water, swallowing contaminated soil, eating food that was packaged in material that contains PFOS, consuming fish from contaminated waters, and breathing in or swallowing dust that contains PFOS.[1-3] Additionally, babies born to mothers exposed to PFOS can be exposed to PFOS during pregnancy and breastfeeding.[1-3]

Chemical Profile

	PFOS
Structure:	
CAS Number:	1763-23-1
Formula:	$C_8HF_{17}O_3S$
Molar Mass:	500.03 g/mol
Synonyms:	Perfluoro-n-octanesulfonic acid Perfluorooctane-1-sulfonic acid Perfluorooctylsulfonic acid 1-Perfluorooctanesulfonic acid Perfluorooctane sulphonic acid Perfluorooctane-sulfonic acid Perfluoro-n-octane sulfonic acid n-Perfluorooctane sulfonic acid Heptadecafluorooctanesulphonic acid Heptadecafluorooctanesulfonic acid Heptadecafluorooctane sulfonic acid Heptadecafluoro-1-octanesulfonic acid Heptadecafluorooctane-1-sulphonic acid Heptadecafluorooctane sulphonic acid

This information was obtained from the PubChem database.[4]

Current Standard

Wisconsin does not currently have NR140 Groundwater Quality Public Health Standards for PFOS.[5]

In 2020, DHS recommended a combined enforcement standard of 20 nanograms per liter (ng/L) for PFOS, perfluorooctanoic acid (PFOA), n-ethyl perfluorooctane sulfonamideoethanol (NEtFOSE), n-ethyl perfluorooctane sulfonamidacetic acid, (NEtFOSAA), n-ethyl perfluorooctane sulfonamide (NEtFOSA), and perfluorooctane sulfonamide (FOSA).

Our recommended standard was based on a modeling approach that estimated how much PFOA a mother had to be exposed to protect the baby from developmental effects. We recommended a combined standard because studies have shown that PFOS and PFOA can cause similar effects in humans and in animals and because NEtFOSE, NEtFOSAA, NEtFOSA, and FOSA breakdown into PFOS in the body and the environment. We recommended a preventive action limit of 2 ng/L – 10% of the enforcement standard – due to carcinogenic, mutagenic, and interactive effects.

These standards, however, were not adopted in rule.[6a]

Standard Development

The process for developing groundwater standards is specified in Wisconsin Stat. ch. 160.[7] To develop recommended public health groundwater standards, we (DHS) gather relevant scientific information, select the appropriate standard based on statutory requirements, and document these findings.

Available Scientific Information for PFOS	
Federal Numbers	
Maximum Contaminant Level (Individual):	**Yes**
Maximum Contaminant Level (Hazard Index):	No
Health Advisory:	No
Drinking Water Concentration (Cancer Risk):	No
State Drinking Water Standard	
NR 809 Maximum Contaminant Level:	**Yes**
Acceptable Daily Intake	
EPA Human Health Toxicity Value:	**Yes**
Oncogenic Potential	
EPA Cancer Slope Factor:	**Yes**
Guidance Values	
ATSDR Chronic Oral Minimum Risk Level:	**Yes**
Technical Information:	
Critical toxicology/epidemiology studies?	No

Federal Numbers

Wisconsin Stat. ch. 160, requires that DHS use the most recent federal number as the recommended enforcement standard.[7] This requirement does not apply if a federal number does not exist or there is significant technical information that was not considered when the federal number was established and this information indicates a different number should be used to set the standard.

Maximum Contaminant Level

In April 2024, the United States Environmental Protection Agency (EPA) established a maximum contaminant level (MCL) of 4 nanograms per liter (ng/L) for PFOS.[8]

The maximum contaminant level (MCL) is the highest level of a substance that is allowed in drinking water served by public water systems as defined by the Safe Drinking Water Act.[8] To establish an MCL, the United States Environmental Protection Agency (EPA) first derives a maximum contaminant level goal (MCLG).[9] The MCLG is the level of a substance at which health effects are not expected to occur allowing for an adequate margin of safety.[9] For substances classified as either "carcinogenic to humans"

a In August 2022, the DNR started a rule-making effort to establish groundwater standards for PFOA, PFOS, PFBS, and HFPO-DA based on DHS' recommendations. In December 2023, this rule package was sent to the state legislature because the estimated economic impact of the proposed changes was more than 20 million dollars, which requires the legislature to approve further action. No additional action on this rule package has been made as of September 2024.

or "likely to be carcinogenic to humans," EPA sets the MCLG at zero because there is no known safe level of exposure for these substances.[10, b]

For substances with an MCLG of zero, the EPA sets the Maximum Contaminant Level (MCL) as close to the MCLG as feasible. In these cases, EPA typically sets the MCL at the practical quantitation limit (PQL).

For PFOS, EPA determined that the PQL is 4 ng/L.[10] As such, the EPA set the MCL for PFOS equal to the PQL of 4 ng/L.

Health Advisory

EPA does not currently have a drinking water health advisory for PFOS.[c]

Drinking Water Concentration (Cancer Risk)

EPA does not have drinking water concentrations based on cancer risk for PFOS.

State Drinking Water Standard

Wisconsin Stat. ch. 160, requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

In 2020, Wisconsin adopted a maximum contaminant level of 70 nanograms per liter for PFOS and PFOA.[11] This standard is based on EPA's 2016 lifetime health advisory.[12]

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. ADIs are sometimes termed oral reference doses by EPA. EPA establishes these ADIs to develop a drinking water health advisory, conduct a human health risk assessment for pesticides, or for use by the Integrated Risk Information System (IRIS) program.

EPA Oral Reference Dose

In 2023, EPA's Office of Research and Development established an oral reference dose of 1×10^{-7} milligrams PFOS per kilogram bodyweight per day (mg/kg-d).[3, 13]

The EPA identified two critical studies that observed associations between PFOS exposure and increased total cholesterol among adults and decreased infant birth weight (**Figure A-1**).[3, 13-15] For each study, EPA

b For these substances, EPA follows the linear default extrapolation approach in establishing the MCLG.[9] This approach assumes that there is a proportional relationship between dose and carcinogenicity at low concentrations that extrapolate to zero. This approach ensures that the MCLG is set at a level where there are no known or anticipated adverse health effects – zero.

c While EPA issued an interim drinking water health advisory for PFOS in 2022, they state that the advisories for PFOS and PFOA "no longer reflect the best available scientific information because they were based on draft noncancer toxicity values from the 2021 SAB review drafts of the PFOA and PFOS toxicity assessments."

used benchmark dose modeling to obtain an internal point of departure (POD) from serum levels (**Table 1**). EPA then used a physiologically based pharmacokinetic (PBPK) model to convert the internal POD to a human-equivalent dose POD, which is the external exposure amount that it would take to result in the internal dose associated with the indicated health outcome.[d] EPA then obtained the oral reference dose by dividing the human equivalent PODs by a total uncertainty factor.

Table 1. Endpoints, Points of Departure, and Uncertainty Factors used by EPA to establish the Oral Reference Dose for PFOS*

Reference	Outcome	Endpoint	$POD_{Internal}$	POD_{HED}	Uncertainty Factors	Reference Dose
Dong et al., 2019 (14)	Increased total cholesterol	$BMDL_{5RD}$	9.34 ng/mL	$1.13x\ 0^{-6}$ mg/kg-d	Interspecies: 1 Intraspecies: 10 Endpoint: 1 Duration: 1 Database: 1 Total: 10	$1x10^{-7}$ mg/kg-d
Wikström et al., 2020 (15)	Decreased birth weight	$BMDL_{5RD}$	7.7 ng/mL	$1.20x10^{-6}$ mg/kg-d	Interspecies: 1 Intraspecies: 10 Endpoint: 1 Duration: 1 Database: 1 Total: 10	1×10^{-7} mg/kg-d

$BMDL_{0.5SD}$ = Lower bound dose corresponding to the 95% lower confidence limit for a change in the mean response equal to 0.5 SD from the control mean; $BMDL_{0.5SD}$ = Lower bound dose corresponding to the 95% lower confidence limit for a 5% change in response

*Adapted from Tables 4-8, 4-9, and 4.11 in EPA's *Human Health Toxicity Assessment for Perfluorooctanoic Acid (PFOA) and Salts*.[3]

Oncogenic Potential

Wisconsin Stat. ch. 160, requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that a substance is carcinogenic and there is no federal number or ADI from the EPA, then we must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of a substance, we looked to see if the EPA, IARC, or another agency has classified the cancer potential of for that substance. If so, we look to see if EPA or another agency has established a cancer slope factor.

d EPA selected the one-compartment human developmental model published by Verner et al. (2016). Details of this model and the adaptations that EPA made are provided in Section 4.1.3 of EPA's *Human Health Toxicity Assessment for Perfluorooctane Sulfonic Acid (PFOS) and Related Salts* Document.[3]

Cancer Classification

As part of their toxicity review, the EPA classified PFOS as "likely to be carcinogenic to humans" based on the evidence of bladder, prostate, liver, kidney, and breast cancers in humans and the increased incidence of tumors and cancers in research animals.[3, 12, 16]

The IARC has classified PFOS as "possibly carcinogenic to humans (Group 2B)." They based this classification on mechanistic data.[17, 18]

EPA Cancer Slope Factor

As part of their toxicity review, the EPA established a cancer slope factor of 39.5 $(mg/kg\text{-}d)^{-1}$ for PFOS in 2024.[3] They established this value from studies by Butenhoff et al. and Thomford that found that PFOS exposure caused liver tumors and cancer in female rats in a dose-dependent manner.[3, 19, 20]

Additional Technical Information

Wisconsin Stat. ch. 160, allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PFOS, we searched for any guidance values that had been published since DHS completed the literature review for PFOS in April 2019 as part of the Cycle 10 Groundwater Standards request. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Reference Level

In 2021, the ATSDR released their final Toxicological Profile for Perfluoroalkyls.[1] In this Profile, they established an intermediate oral minimum risk level of 2×10^{-6} mg/kg-d for PFOS.[e]

ATSDR selected a two-generation reproduction study by Luebker et al. as the critical study.[1, 21] In this study, male and female rats were exposed to PFOS prior to and during mating and through gestation and lactation across two generations. The ATSDR identified a lowest observable adverse effect level (LOAEL) of 0.4 mg/kg-d based on delayed eye opening in first generation offspring and transient decreases in second generation offspring body weight during lactation at this dose.

e The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not establish a chronic oral MRL for PFOS because they did not identify chronic duration studies and their policy is to not extrapolate across exposure durations.

ATSDR then used a PBPK model to estimate a human equivalent dose of 0.000515 mg/kg-d and applied a total uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (3), and using a LOAEL instead of a NOAEL (10).[f]

Literature Search

To ensure that Wisconsin's public health groundwater standards are established based on the best available information, DHS searches for relevant health studies published after the last literature review completed for a health value from the EPA.[g] We used the Web of Science and PubMed databases to look for studies that related to toxicity, effects on a disease state, and the key health effects of genotoxicity, carcinogenicity, teratogenicity, and interactivity for use in establishing the appropriate preventive action limit.

We excluded studies that did not meet the Population, Exposure, Comparator, and Outcome (PECO) criteria described in **Table A-1**. After applying these exclusion criteria, we located four key toxicity studies (**Table A-2**) and 72 key epidemiological studies (**Supplemental Table**).

Critical Toxicology Studies

To be considered a critical toxicity study, the study must have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have the appropriate toxicity and pharmacokinetic information necessary to establish an ADI (i.e., identifiable toxicity value, measured serum concentrations, reported half-life).

None of the key toxicity studies meet the critical toxicity study criteria (**Table A-2**).

Critical Epidemiological Studies

To be considered a critical epidemiology paper, the study must contain dose-response data in a format that can be used to establish an acceptable daily intake (i.e., established benchmark dose level) or the study must evaluate the impact of exposure at various concentrations of the substance in drinking water.

None of the key epidemiology studies met these criteria (**Supplemental Table**).

Key Health Studies

Wisconsin Stat. ch. 160, states that DHS must recommend a preventive action limit of 10% of the enforcement standard for substances that have carcinogenic, mutagenic, teratogenic, or interactive effects.[7]

To recommend the appropriate preventive action limit, we reviewed the available scientific information for evidence of the ability for PFOS to cause these key health effects.

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f ATSDR used a PBPK model published by Wambaugh et al. in 2013 to convert the level of PFOS in animal serum to a level in serum that would cause the same effect in humans. Details of the model and the parameters that ATSDR used in their analysis are provided in Appendix A of the *Toxicological Profile for Perfluoroalkyls*.

g The last literature search completed by EPA was in February 2023 by the Integrated Risk Information System program in their work to establish a draft oral refence dose for PFOA.

Carcinogenicity

As noted above, the EPA has classified PFOS as likely to be carcinogenic to humans.[3, 12, 16] This classification is based on data from epidemiological studies among people and toxicity studies in research animals.

Key Health Effects for Establishing the Preventive Action Limit	
Carcinogenic:	Evidence indicates that the substance can produce or incite cancer.
Mutagenic:	Evidence indicates that the substance can alter or damage DNA.
Teratogenic:	Evidence indicates that the substance can cause structural defects in unborn babies.
Interactive:	Evidence indicates that the substance can increase the toxicity of other substances or that the substance's toxicity can be increased by the presence of other substances.

Mutagenicity

In their toxicology review, EPA found mixed results on the potential for PFOS to cause mutagenic effects were mixed – based on the available studies. Of note was a study by Governini et al. that observed a significant increase in the DNA fragmentation of sperm in individuals with measurable levels of PFOS.[22]

They also found several studies in research animals that found that PFOS exposure caused DNA damage and micronuclei formation in bone marrow and peripheral blood cells.[23-25] In our literature review, we found a study by Spyrou et al. in human lymphocyte cells in which PFOS exposure caused a dose-dependent increase in micronuclei frequency.[26]

Teratogenicity

In their toxicology review, EPA identified several studies that reported teratogenic effects in research animals.[3, 27-29] For example, Yahia et al. found that PFOS caused statistically significant increases in the numbers of fetuses with cleft palates, sternal defects, wavy ribs, spina bifida in the offspring of mice exposed during pregnancy.[28] We did not find any additional studies on teratogenic effects in our literature search.

Interactivity

In their toxicology review, EPA identified that co-exposure to mixtures of PFAS, including PFOS, can produces dose-additive effects.[30, 31] They also found that many PFAS, including PFOS, cause health effects through the same processes – for instance by affecting thyroid hormone signaling or impacting immune and liver function.[30, 31] In our literature search, we found numerous epidemiological studies that observed similar effects with PFAS mixtures containing PFOS.[32-48]

Standard Selection

Basis for Enforcement Standard

- ☒ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

DHS recommends an enforcement standard of 4 ng/L for PFOS.

State statute requires that DHS recommend a federal number (such as a maximum contaminant level, health advisory, drinking water concentration based on

cancer risk) if one is available and there is no significant technical information to indicate that a different value is more appropriate.

The EPA's maximum contaminant level (MCL) for PFOS was established in April 2024 with their last scientific review completed in February 2023. In our review of toxicological and epidemiological information published since this time, we did not identify significant findings indicating that a value other than the MCL should be used to establish the enforcement standard.

DHS recommends a preventive action limit of 0.4 ng/L for PFOS.

DHS recommends that the preventive action limit for PFOS be set at 10% of the enforcement standard because studies have shown that PFOS can cause carcinogenic, mutagenic, teratogenic, and interactive effects.

Prepared by Sarah Yang, PhD with assistance from Becky Bowen, MPH, MS

Wisconsin Department of Health Services

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Appendix A: Literature Review Details

Table A-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria for PFOS Study Evaluation

Element	Toxicological Inclusion Criteria	Epidemiological Inclusion Criteria
Population:	Non-human mammalian animal species (whole organism) of any life-stage (including preconception, in utero, lactation, peripubertal, and adult stages).	Any population and life-stage (occupational or general population, including children and other sensitive populations).
Exposure:	Any exposure to PFOS only via oral routes for at least 28 days*	Any exposure to PFOS via oral routes.
Comparator:	A concurrent control group exposed to vehicle-only treatment or untreated control.	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of PFOS or exposure to PFOS for shorter periods of time.
Outcome:	All health outcomes	All health outcomes.

*Exceptions are studies that are conducted during reproduction and/or development.

This literature search was conducted in the National Institutes of Health's *PubMed* resource and Clarivate Analytics' *Web of Science* resource. We used the following search terms in the literature review:

Title/abstract: PFOS or "perfluorooctane sulfonate" and the synonyms listed in Chemical Properties table
Subject area: toxicology, public environmental occupational health (Web of Science)
MeOH search terms: toxicology, epidemiology, public health (PubMed)
Language: English

Table A-2. PFOS Key/Critical Toxicity Studies

Reference	Exposure	Key Findings	Critical Toxicity Criteria	Relevant Toxicity Data	Uncertainty Factors	Candidate ADI
An et al., 2023[49]	Mice were exposed to 0, 0.3, 1, 3 mg/kg-d PFOS through gavage for 84 days.	PFOS caused depressive-like behaviors in males. PFOS increased glutamate and proline levels and decreased glutamine and tryptophan levels.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 0.3 mg/kg-d POD_{HED}: N/A	N/A	N/A
Yen et al., 2024[50]	Male rats were exposed to 0, 5, and 10 mg/kg-d PFOS through gavage for 21 days.	PFOA decreased body weight gain and increased relative liver in a dose-dependent manner. PFOA also altered lipid profiles in the liver, kidney, and testes.	☒ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI	NOAEL: N/A LOAEL: 5 mg/kg-d POD_{HED}: N/A	N/A	N/A
Ling et al., 2024[51]	Male mice were exposed to 0, 1, 5, 10 mg/kg-d PFOS through gavage for 28 days and given either a low or high fat diet before and during exposure.	In mice given high fat diet the highest dose of PFOA increased relative liver weight, liver TG and both doses increased levels of the liver enzymes ALT and AST.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: 1 mg/kg-d LOAEL: 5 mg/kg-d POD_{HED}: N/A	N/A	N/A
Dangudubiyyam, et al., 2024[52]	Pregnant rats were exposed to 0, 10, and 50 µg/mL PFOS through drinking water from GD 4-20.	PFOS decreased fetal and placental weight in a dose-dependent manner. PFOS altered levels of several reproductive hormones.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 10 µg/mL POD_{HED}: N/A	N/A	N/A

ACO: Peroxisomal Acyl-CoA oxidase (ACO) activity – a measure of peroxisome proliferation and peroxisomal enzymatic activities; PROD: Pentoxyresorufin-O-dealkylase – a measure of microsomal enzymatic activity indicating constitutive androstane receptor (CAR) activation in the liver; PBS: phosphate buffer solution; TMEV: Theiler's murine encephalomyelitis virus - naturally occurring murine virus used to model human neurological symptoms associated with viral infections; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Figure A-1. EPA's Process for Selecting the Final Oral Reference Dose for PFOS

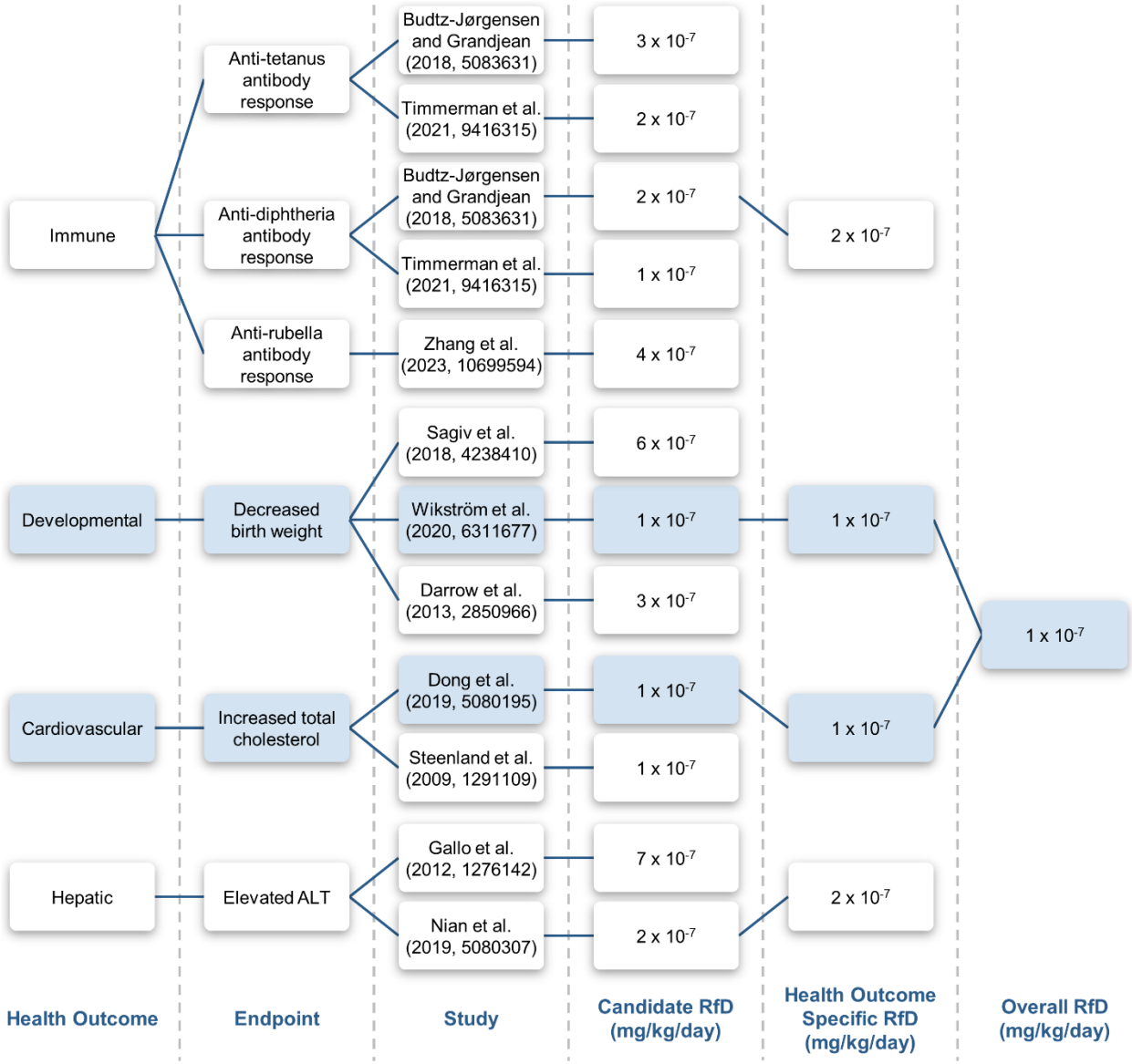


Figure 4-5 in EPA's *Human Health Toxicity Assessment for Perfluorooctane Sulfonic Acid (PFOS) and Related Salts*[3]

PFNA | 2024

Substance Overview

Perfluorononanoic acid (PFNA) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS).[1, 2] PFNA is made up of nine carbon-fluorine bonds and a carboxylic acid group. Because PFNA contains more than six carbon-fluorine bonds, it is considered a long-chain PFAS.[1, 2] Long-chain PFAS, like PFNA, stay in the human body for a long time.[1, 2]

PFNA has been used primarily to make polyvinylidene fluoride – a compound designed to be both temperature resistant and nonreactive.[1, 2] Polyvinylidene fluorides are used as insulation for wire and circuit boards, as well as valves, and pipes.[1, 2] Teflon™ is a type of polyvinylidene fluoride.

Recommendations

DHS recommends a Public Health Groundwater Enforcement Standard for PFNA set at 10 nanograms per liter (ng/L). The recommended standard is based on the individual maximum contaminant level (MCL) that the United State Environmental Protection Agency (EPA) established for PFNA in 2024. DHS recommends that the Public Health Groundwater Preventive Action Limit for PFNA be set at 10% of the enforcement standard because PFNA has been shown to cause mutagenic and interactive effects.

Recommended Standards	
Enforcement Standard:	10 ng/L
Preventive Action Limit:	1 ng/L

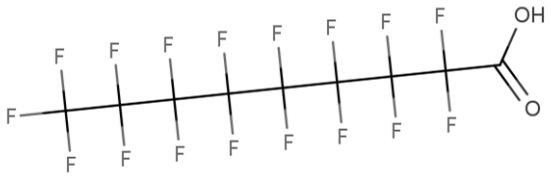
Health Effects

Studies among people and in research animals indicate that exposure to PFNA can impact development.[1, 2] Additionally, studies among people and in research animals suggest that PFNA may impact immune response, neurodevelopment, the cardiovascular system, and the thyroid.[1, 2]

Exposure Routes

People can be exposed to PFNA by drinking contaminated water, swallowing contaminated soil, consuming fish from contaminated waters, and breathing in or swallowing dust that contains PFNA.[1, 2] Babies born to mothers exposed to PFNA can be exposed to PFNA during pregnancy and breastfeeding.[1, 2]

Chemical Profile

	PFNA
Structure:	
CAS Number:	375-95-1
Formula:	$C_9HF_{17}O_2$
Molar Mass:	464.08 g/mol
Synonyms:	Perfluorononanoic acid Heptadecafluorononanoic acid Perfluoro-n-nonanoic acid Perfluorononan-1-oic acid Heptadecafluoropelargonic acid 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-Heptadecafluoro-nonanoic acid

Information obtained from the PubChem database.[3]

Current Standards

Wisconsin does not currently have NR140 Groundwater Quality Public Health Standards for PFNA.[4]

In 2020, DHS recommended an enforcement standard of 30 nanograms per liter (ng/L) for PFNA.[5] The recommended standard is based on a research study that found that PFNA can cause reproductive toxicity in rodents. We also recommended a preventive action limit of 3 ng/L – 10% of the enforcement standard – due to interactive effects with endocrine disrupting chemicals in research animals. These standards, however, were not adopted in rule.[6]

Standards Development

The process for developing groundwater standards is specified in Chapter 160, Wis. Stats.[7] To develop recommended public health groundwater standards, we (DHS) gather relevant scientific information, select the appropriate standard based on statutory requirements, and document these findings.

Available Scientific Information for PFNA	
Federal Numbers	
Maximum Contaminant Level (Individual):	**Yes**
Maximum Contaminant Level (Hazard Index):	**Yes**
Health Advisory:	No
Drinking Water Concentration (Cancer Risk):	No
State Drinking Water Standard	
NR 809 Maximum Contaminant Level:	No
Acceptable Daily Intake	
EPA Oral Reference Dose (DRAFT):	**Yes**
Oncogenic Potential	
EPA Cancer Slope Factor:	No
Guidance Values	
ATSDR Chronic Oral Minimum Risk Level:	**Yes**
Technical Information	
Critical toxicology or epidemiology studies:	No

Federal Numbers

Wisconsin Stat. ch. 160, requires that DHS use the most recent federal number as the recommended enforcement standard.[7] This requirement does not apply if a federal number does not exist or there is significant technical information that was not considered when the federal number was established and this information indicates a different number should be used to set the standard.

Maximum Contaminant Level (Individual)

The maximum contaminant level (MCL) is the highest level of a substance that is allowed in drinking water served by public water systems as defined by the Safe Drinking Water Act.[8, 9] To establish an MCL, the United States Environmental Protection Agency (EPA) first derives a maximum contaminant level goal (MCLG).[10] The MCLG is the level of a substance at which health effects are not expected to occur allowing for an adequate margin of safety.[10]

In April 2024, the EPA established an individual MCL for PFNA of 10 nanograms per liter (ng/L).[2, 11] The EPA set the MCL for PFNA equal to its MCLG. The EPA established the MCLG for PFNA using the Agency for Toxic Substances and Disease Registry's (ATSDR's) intermediate-duration oral minimum risk level (MRL) (Equation 1).[1, 2, a]

a The EPA did not use the oral reference dose proposed by IRIS in 2023 to establish the MCLG because it was not a finalized when they were establishing the MCLs. [9] In their response to comments, the EPA stated that "the ATSDR minimal risk levels for…PFNA currently represent the best available, peer-reviewed science…"

Equation 1: $$\text{MCLG} = \frac{\text{Health Based Water Concentration}}{\text{Drinking water Intake}_{\text{BWI}}} \text{ x Relative Source Contribution}$$

Where: Health Based Water Concentration = 3 x 10^{-6} mg/kg-d
EPA used ATSDR's intermediate duration oral MRL (see *Technical Information* section for more details).
Daily Water Intake (Body Weight Adjusted) = 0.0469 L/kg/day
90th percentile direct and indirect consumption of community water, consumer-only 2-day average, lactating people.
EPA selected this value because it is protective of people who are pregnant and people who are breastfeeding.
Relative Source Contribution = 0.2
EPA used the default value; their literature search found that available information does not allow for the quantitative characterization of the relative levels of exposure among these different sources.

Maximum Contaminant Level (Hazard Index)

The EPA also established a Hazard Index Maximum Contaminant Level which includes PFNA. [2, 11] The hazard index is an approach used to account for the risk to exposure to combined and co-occurring levels of these PFAS in drinking water. The EPA's Hazard Index MCL is set at 1 and applies to any mixture that contains two or more of HFPO-DA (GenX), PFBS, PFNA, and PFHxS.

The Hazard Index MCL compares the level of each PFAS measured in the water to its health-based water concentration – which is either the individual MCLG or the health advisory in the case of PFBS (Equation 2).[b]

Equation 2: $$\text{Hazard Index} = \frac{\text{HFPO-DA Level}}{\text{HFPO-DA MCL}} + \frac{\text{PFBS Level}}{\text{PFBS HA}} + \frac{\textbf{PFNA Level}}{\textbf{PFNA MCL}} + \frac{\text{PFHxS Level}}{\text{PFHxS MCL}}$$

Where: The "Level" is the concentration of the PFAS detected in public drinking water.
GenX MCL = 10 ng/L
PFBS HA = 2000 ng/L
PFNA MCL = 10 ng/L
PFHxS MCL = 10 ng/L

HFPO-DA = Hexafluoropropylene oxide dimer acid (also referred to as GenX); PFBS = perfluorobutanesulfonic acid; PFHxS =perfluorohexanesulfonic acid; MCLG = maximum contaminant level goal; HA = drinking water health advisory

Units: ng/L = nanograms PFAS per liter water

Health Advisory

The EPA has not established a drinking water health advisory for PFNA.

b In their *Response to Comments on the National Primary Drinking Water Standards*, the EPA stated that they decided to defer establishing an individual MCL for PFBS until there is more information on the likelihood that PFBS will individually occur in public water systems and at a level of public health concern.[9]

Drinking Water Concentration (Cancer Risk)

When establishing the MCL, EPA stated that they had not yet completed a final evaluation and classification of the carcinogenicity of PFNA.[2] In their draft IRIS review of PFNA, EPA determined that there were not enough carcinogenicity data to establish a drinking water concentration based on a cancer risk level for PFHxS.[12, 13]

State Drinking Water Standard

Wisconsin Stat. ch. 160, requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.[7]

NR 809 Maximum Contaminant Level

Wisconsin does not have a drinking water standard for PFNA.[14]

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, Ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation.[7] Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. ADIs are sometimes termed oral reference doses by EPA. EPA establishes these ADIs to develop a drinking water health advisory, conduct a human health risk assessment for pesticides, or for use by the Integrated Risk Information System (IRIS) program.

EPA Oral Reference Dose (Draft)

In 2024, the EPA's Integrated Risk Information System (IRIS) derived a draft oral reference dose of 7 x 10^{-9} milligrams of PFNA per kilogram bodyweight per day (mg/kg-d).[12]

For the critical study, EPA selected a meta-analysis by Wright et al. in which the researchers evaluated the association between PFNA and birth weight.[12, 15] From this study, the EPA used the benchmark dose at the lower confidence interval (BMDL) of 10 studies to derive the draft oral reference dose (Equation 3).

Equation 3: $$\text{Reference Dose (Draft)} = \frac{\text{Point of Depature - Human Equivalent Dose}}{\text{Total Uncertainty Factor}}$$

Where: Point of Departure - Human Equivalent Dose =
Internal Point of Departure x Clearance Rate

Point of Departure – Internal = 1.81 x 10^{-3} mg/L PFNA in serum
For this, EPA used the benchmark dose at half standard deviation ($BMDL_{1/2SD}$).

Clearance Rate = 0.124 mL/kg-d
For this, EPA used the estimated clearance rate for females of reproductive age.

Total Uncertainty Factor = Intraspecies x Database

EPA used a Total Uncertainty Factor of 30.
They selected an *intraspecies uncertainty factor* (UF_H) of 10 to account for interindividual differences in human susceptibility.

They selected a *database uncertainty factor* (UF_D) of 3 to account for deficiencies in the toxicity evidence base.

Oncogenic Potential

Wisconsin Stat. ch. 160, requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard.[7] If we determine that a substance is carcinogenic and there is no federal number or ADI from the EPA, then we must set the standard at a level that would result in a cancer risk equivalent to one case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than one in 1,000,000.

To evaluate the oncogenic potential of a substance, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of that substance. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

When establishing the MCL, EPA stated that they had not yet completed a final evaluation and classification of the carcinogenicity of PFNA.[2] In their draft IRIS review of PFNA, the EPA determined that there was inadequate information to assess carcinogenic potential for PFNA by both oral and inhalation routes of exposure.[12] They based this determination on a lack of adequate carcinogenicity data.

The IARC have not evaluated the carcinogenicity of PFNA.[16]

EPA Cancer Slope Factor

Due to the lack of adequate carcinogenicity data, the EPA has not established a cancer slope factor for PFNA.[12]

Additional Technical Information

Wisconsin Stat. ch. 160, allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.[7]

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PFNA, we searched for any guidance values that had been published since DHS completed the literature review for PFNA in August 2020 as part of the Cycle 11 Groundwater Standards request. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Reference Level

In 2021, the ATSDR released their final Toxicological Profile for Perfluoroalkyls in which they established an intermediate oral minimum risk level (MRL) of 3 x 10^{-6} mg/kg-d for PFNA.[1, c]

For the critical study, ATSDR selected a 2015 toxicity study in mice by Das et al.[1, 17] In this study, mice were exposed to different concentrations of PFNA (0, 1, 3, 5, and 10 mg/kg-d) from gestational days 1 to 17 through gavage. For the toxicity value, ATSDR selected a No Observable Adverse Effect Level (NOAEL) of 1 mg/kg-d based on the developmental effects observed in offspring at the higher doses. They established the MRL using a human equivalent dose (HED), a total uncertainty factor, and a modifying factor (Equation 4).

Equation 4:

$$\text{Minimum Risk Level} = \frac{\text{Human Equivalent Dose}}{\text{Total Uncertainty Factor} \times \text{Modifying Factor}}$$

Where: Human Equivalent Dose = 0.0001 mg/kg-d
Estimated by ATSDR from measured serum concentrations in animals using the trapezoid rule (described in more detail in **Appendix B**).

Total Uncertainty Factor = Interspecies x Intraspecies
ATSDR used a total uncertainty factor of 30.
They selected an *interspecies uncertainty factor* (UF_S) of 3 to account for the extrapolation of data from animals to humans with dosimetric adjustments.
They selected an *intraspecies uncertainty factor* (UF_H) of 10 to account for the interindividual differences in human susceptibility.

Modifying Factor (MF) = 10
ATSDR added this factor to account for database limitations.

Literature Search

To ensure that Wisconsin's public health groundwater standards are established based on the best available information, DHS searches for relevant health studies published after the last literature review completed for a health value from the EPA.[d] For PFNA, we used the Web of Science and PubMed databases to look for studies that related to toxicity, effects on a disease state, and the key health effects of genotoxicity, carcinogenicity, teratogenicity, and interactivity for use in establishing the appropriate preventive action limit.

We excluded studies that did not meet the Population, Exposure, Comparator, and Outcome (PECO) criteria described in **Table A-1**. After applying these exclusion criteria, we did not locate any key toxicity studies, but we located 77 key epidemiological studies (**Supplemental Table**).

Critical Epidemiological Studies

To be considered a critical epidemiology paper, the study must contain dose-response data in a format that can be used to establish an acceptable daily intake (i.e., established benchmark dose level) or the

c The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not establish a chronic oral MRL for PFNA because they did not identify chronic duration studies and their policy is to not extrapolate across exposure durations.

d The last literature search completed by EPA was in April 2023 by the Integrated Risk Information System program in their work to establish a draft oral refence dose for PFNA.

study must evaluate the impact of exposure at various concentrations of the substance in drinking water.

None of the key epidemiological studies met these criteria (**Supplemental Table**).

Key Health Studies

Wisconsin Stat. ch. 160, states that DHS must recommend a preventive action limit of 10% of the enforcement standard for substances that have carcinogenic, mutagenic, teratogenic, or interactive effects.[7] To recommend the appropriate preventive action limit, we reviewed the available scientific information for evidence that PFNA can cause these key health effects.

Key Health Effects for Establishing the Preventive Action Limit	
Carcinogenic:	Evidence indicates that the substance can produce or incite cancer.
Mutagenic:	Evidence indicates that the substance can alter or damage DNA.
Teratogenic:	Evidence indicates that the substance can cause structural defects in unborn babies.
Interactive:	Evidence indicates that the substance can increase the toxicity of other substances or that the substance's toxicity can be increased by the presence of other substances.

Carcinogenicity

When establishing the MCL, EPA reviewed several epidemiological studies that examined the association between PFNA exposure and cancer risk and noted that there were no consistent associations between PFNA exposure and breast or prostate cancer risk.[2] While establishing the draft oral reference dose, EPA reviewed seven additional studies.[12] They determined that four studies were uninformative and two had low confidence.[12, 18] The single medium confidence study found no clear positive association between PFNA exposure and breast cancer.[12, 18, 19] Additionally, there are no long-term carcinogenicity studies in research animals. In our literature search, we found evidence of potential carcinogenic effects in a handful of studies.[20-23]

Mutagenicity

In their review, ATSDR identified one study in human liver cells that found that PFNA caused a "modest increase" in DNA damage.[1, 24] While establishing the draft oral reference dose, EPA identified one study in research animals and several studies in cell cultures that found that PFNA exposure caused DNA damage responses.[12, 25-27] In our literature search, we did not locate any additional studies examining the genotoxic effects of PFNA.

Teratogenicity

While establishing the draft oral reference dose, EPA noted that there was some suggestive evidence of associations between PFNA and birth defects.[12, 13, 28, 29] However, the study that saw evidence of associations EPA considered a low confidence study due deficiencies in participant selection, outcome ascertainment, exposure sensitivity, and possible confounding.[12, 28] In our literature search, we did not locate any additional studies examining the teratogenic effects of PFNA.

Interactivity

The EPA established the hazard index MCL on the basis that co-exposure to mixtures of PFAS can produces dose-additive effects.[2, 11] These mixtures included PFNA. In establishing this approach, they also noted that data show that many PFAS, including PFNA, cause health effects through the same processes – for instance by affecting thyroid hormone signaling or impacting immune and liver function.[2, 11] We found similar responses in our literature search.[30-43]

Standard Selection

DHS recommends an enforcement standard of 10 ng/L for PFNA.

State statute requires that DHS recommend a federal number (such as a maximum contaminant level, health advisory, drinking water concentration based on cancer risk) if one is available and there is no significant technical information to indicate that a different value is more appropriate.

Basis for Enforcement Standard

- ☒ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

The EPA's maximum contaminant level (MCL) for PFNA was established in April 2024 with their last scientific review completed in April 2023. In our review of toxicological and epidemiological information published since this time, we did not identify significant findings indicating that a value other than the MCL should be used to establish the enforcement standard.

DHS recommends a preventive action limit of 1 ng/L for PFNA.

DHS recommends that the preventive action limit for PFNA be set at 10% of the enforcement standard because studies have shown that PFNA can cause mutagenic and interactive effects.

Prepared by Sarah Yang, PhD with assistance from Becky Bowen, MPH, MS

Wisconsin Department of Health Services

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Appendix A: Literature Review Details

Table A-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria for PFNA Study Evaluation

Element	Toxicological Inclusion Criteria	Epidemiological Inclusion Criteria
Population:	Non-human mammalian animal species (whole organism) of any life-stage (including preconception, in utero, lactation, peripubertal, and adult stages).	Any population and life-stage (occupational or general population, including children and other sensitive populations).
Exposure:	Any exposure to PFNA only via oral routes for at least 28 days*	Any exposure to PFNA via oral routes.
Comparator:	A concurrent control group exposed to vehicle-only treatment or untreated control.	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of PFNA or exposure to PFNA for shorter periods of time.
Outcome:	All health outcomes	All health outcomes.

*Exceptions are studies that are conducted during reproduction and/or development.

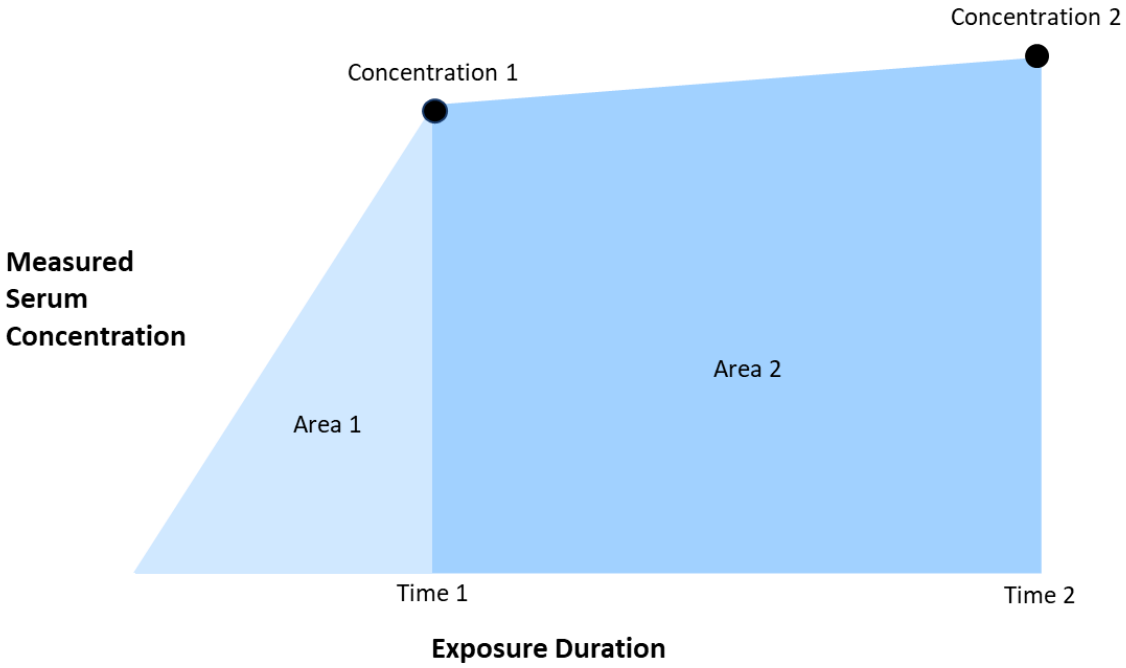
This literature search was conducted in the National Institutes of Health's *PubMed* resource and Clarivate Analytics' *Web of Science* resource. We used the following search terms in the literature review:

Title/abstract: PFNA or "perfluorononanoic acid" (also synonyms listed in Chemical Properties table)
Subject area: toxicology, public environmental occupational health (Web of Science)
MeOH search terms: toxicology, epidemiology, public health (PubMed)
Language: English

Appendix B. Calculation of Human Equivalent Dose

To calculate the human equivalent dose for PFNA, we followed a three-step process.

1. We first calculated the area under the curve at the selected toxicity value using the trapezoid rule.



In this mathematical approach, the area under the curve is divided into one or more trapezoids and area of each trapezoid is calculated (Equation B-1).

Equation B-1

$$\text{Area} = \frac{h}{2}(p+q)$$

Where:

h = The difference in time between the data points.
q = Measured serum concentration at first time point
p = Measured serum concentration at second time point

The areas of all of the trapezoids are summed to give the area under the curve (Equation B-2).

Equation B-2

$$\text{AUC} = \text{Area}_1 + \text{Area}_2 + \ldots + \text{Area}_n$$

2. We then calculated the time-weight average serum concentration as a surrogate for the steady-state serum concentration (Equation B-3).

Equation B-3

$$\text{TWA} = \frac{\text{AUC}}{\text{ED}}$$

Where:

AUC = The difference in time between the data points.
ED = Exposure duration (days)

3. Finally, we calculated the human equivalent dose (HED) by accounting for the long half-life in people.

$$HED = \frac{TWA \times \frac{\ln 2}{t_{1/2}} \times V_d}{AF}$$

Where:

$t_{1/2}$ = Half-life – measure of measure of a substance's elimination rate.
ATSDR used a value of 900 days from data in young females.

V_d = Volume of distribution - theoretical volume needed to contain the amount of the substance administered at the measured serum concentration.
ATSDR used a value of 0.2 L/kg based on studies in nonhuman primates.

AF = Gastrointestinal absorption fraction - measure how much of the chemical is available to cause harm within the body.
ATSDR used a value of 1 based on studies in rodents and non-human primates.

More information on these values is available in ATSDR's *Toxicological Profile for Perfluoroalkyls* – Appendix A.

PFHxS | 2024

Substance Overview

Perfluorohexanesulfonic acid (PFHxS) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS).[1, 2] PFHxS is made up of six carbon-fluorine bonds and a sulfonic acid group.[1, 2] Because PFHxS contains six carbon-fluorine bonds, it is considered a long-chain PFAS.[1, 2] Long-chain PFAS, like PFHxS, stay in the human body for a long time.[1, 2] PFHxS is used to make other PFAS.[1, 2] PFHxS is also found in older fighting-fire foams and some stain repellants.[1, 2]

Recommendations

DHS recommends a Public Health Enforcement Standard of 10 nanograms per liter (ng/L) for PFHxS. The recommended standard is based on the individual maximum contaminant level (MCL) that the United States Environmental Protection Agency (EPA) established for PFHxS in 2024. DHS recommends that the Public Health Preventive Action Limit for PFHxS be set at 10% of the enforcement standard because PFHxS has been shown to cause interactive effects.

Recommended Standards	
Enforcement Standard:	10 ng/L
Preventive Action Limit:	1 ng/L

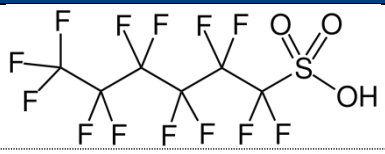
Health Effects

Studies among people and studies in research animals indicate that exposure to PFHxS can impact the thyroid – these studies have shown that PFHxS can lower thyroid hormone levels and may affect the thyroid's weight and structure.[1, 2] Additionally, studies among people indicate that PFHxS exposure may impact the immune system – specifically studies have shown PFHxS levels in children lower antibody response to tetanus and diphtheria vaccines.[1, 2] Additional studies indicate that PFHxS exposure may also affect development and may also impact the liver, brain, and cardiovascular systems.[1, 2]

Exposure Routes

People can be exposed to PFHxS by drinking contaminated water, swallowing contaminated soil, eating food that was packaged in material that contains PFHxS, consuming fish from contaminated waters, and breathing in or swallowing dust that contains PFHxS.[1-3] Babies born to mothers exposed to PFHxS can be exposed to PFHxS during pregnancy and breastfeeding.[1-3]

Chemical Profile

	PFHxS
Structure:	
CAS Number:	355-46-4
Formula:	$C_6HF_{13}O_3S$
Molar Mass:	400.11 g/mol
Synonyms:	Perfluorohexanesulfonic acid 1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexane-1-sulfonic acid Perfluorohexane-1-sulphonic acid Perfluorohexane sulfonic acid Tridecafluorohexane-1-sulfonic acid Perfluorohexanesulphonic acid Perfluorohexane sulfonate Perfluorohexane-1-sulfonic acid Tridecafluorohexanesulfonic acid 1-Perfluorohexanesulfoanic acid

This information was obtained from the PubChem database.[4]

Current Standards

Wisconsin does not currently have NR140 Groundwater Quality Public Health Standards for PFHxS.[5]

In 2020, DHS recommended an enforcement standard of 40 nanograms per liter (ng/L) for PFHxS.[6] The recommended standard was based on a study in research animals that found that PFHxS exposure caused reproductive toxicity. We also recommended a preventive action limit of 4 ng/L – 10% of the enforcement standard – due to interactive effects with endocrine disrupting chemicals in research animals. These standards, however, were not adopted in rule.[7]

Standards Development

The process for developing groundwater standards is specified in Wisconsin Stat. ch. 160.[8] To develop recommended public health groundwater standards, we (DHS) gather relevant scientific information, select the appropriate standard based on statutory requirements, and document these findings.

Available Scientific Information for PFHxS	
Federal Numbers	
Maximum Contaminant Level (Individual):	**Yes**
Maximum Contaminant Level (Hazard Index):	**Yes**
Health Advisory:	No
Drinking Water Concentration (Cancer Risk):	No
State Drinking Water Standard	
NR 809 Maximum Contaminant Level:	No
Acceptable Daily Intake	
EPA Oral Reference Dose (DRAFT):	**Yes**
Oncogenic Potential	
EPA Cancer Slope Factor:	No
Guidance Values	
ATSDR Chronic Oral Minimum Risk Level:	**Yes**
Technical Information:	
Critical toxicology or epidemiology studies identified?	**Yes**

Federal Numbers

Wisconsin Stat. ch. 160, requires that DHS use the most recent federal number as the recommended enforcement standard.[8] This requirement does not apply if a federal number does not exist or there is significant technical information that was not considered when the federal number was established and this information indicates a different number should be used to set the standard.

Maximum Contaminant Level (individual)

In April 2024, the EPA established an individual MCL for PFHxS of 10 ng/L.[2, 9]

The maximum contaminant level (MCL) is the highest level of a substance that is allowed in drinking water served by public water systems as defined by the Safe Drinking Water Act.[10] To establish an MCL, the United States Environmental Protection Agency (EPA) first derives a maximum contaminant level goal (MCLG).[11] The MCLG is the level of a substance at which health effects are not expected to occur allowing for an adequate margin of safety.[11]

The EPA set the MCL for PFHxS equal to its MCLG. The EPA established the MCLG for PFHxS using the Agency for Toxic Substances and Disease Registry's (ATSDR's) intermediate-duration oral minimum risk level (MRL) (Equation 1).[1, 2a]

a The EPA did not use the oral reference dose proposed by IRIS in 2023 to establish the MCLG because it was not a finalized at the time that EPA was establishing the MCLs. In their response to comments, the EPA stated that "the ATSDR minimal risk levels for PFHxS and PFNA currently represent the best available, peer-reviewed science…"

Equation 1: $$MCLG = \frac{\text{Health Based Water Concentration}}{\text{Drinking water Intake - Body Weight Adjusted}} \text{ x Relative Source Contribution}$$

Where: Health Based Water Concentration = 2 x 10^{-6} mg/kg-d

EPA used ATSDR's intermediate duration oral MRL and applied an additional uncertainty factor of 10 to protect sensitive populations.

Daily Water Intake (Body Weight Adjusted) = 0.034 L/kg-d

90th percentile direct and indirect consumption of community water, consumer-only 2-day average, adults 21 years and older – EPA selected this value because the critical effect on which MRL was based was observed in adult male rats.

Relative Source Contribution = 0.2

EPA used the default value; their literature search found that available information does not allow for the quantitative characterization of the relative levels of exposure among these different sources.

Units: mg/kg-d = milligrams PFHxS per kilogram body weight per day
L/kg-d = liters of water per kilogram body weight per day

Maximum Contaminant Level (Hazard Index)

The EPA also established a Hazard Index Maximum Contaminant Level which includes PFHxS.[2, 9] The hazard index is an approach used to account for the risk to exposure to combined and co-occurring levels of these PFAS in drinking water. The EPA's Hazard Index MCL is set at 1 and applies to any mixture that contains two or more of HFPO-DA (GenX), PFBS, PFNA, and PFHxS.

The Hazard Index MCL compares the level of each PFAS measured in the water to its health-based water concentration – which is either the individual MCLG or the health advisory in the case of PFBS (Equation 2).

Equation 2: $$\text{Hazard Index} = \frac{\text{HFPO-DA Level}}{\text{HFPO-DA MCLG}} + \frac{\text{PFBS Level}}{\text{PFBS HA}} + \frac{\text{PFNA Level}}{\text{PFNA MCLG}} + \frac{\textbf{PFHxS Level}}{\textbf{PFHxS MCLG}}$$

Where: The "Level" is the concentration of the PFAS detected in public drinking water.
GenX MCL = 10 ng/L
PFBS HA = 2000 ng/L
PFNA MCL = 10 ng/L
PFHxS MCL = 10 ng/L

Abbreviations: HFPO-DA = hexafluoropropylene oxide dimer acid (also referred to as GenX); PFBS = perfluorobutanesulfonic acid; PFNA = perfluorononanoic acid; MCLG = maximum contaminant level goal; HA = drinking water health advisory

Units: ng/L = nanograms PFAS per liter water

Health Advisory

The EPA has not established a drinking water health advisory for PFHxS.

Drinking Water Concentration (Cancer Risk)

In their draft IRIS review of PFHxS (described below), EPA determined that there were not enough carcinogenicity data to establish a drinking water concentration based on a cancer risk level for PFHxS.[12]

State Drinking Water Standard

Wisconsin Stat. ch. 160, requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.[8]

NR 809 Maximum Contaminant Level

Wisconsin does not have a drinking water standard for PFHxS.

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, Ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation.[8] Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. ADIs are sometimes termed oral reference doses by EPA. EPA establishes these ADIs to develop a drinking water health advisory, conduct a human health risk assessment for pesticides, or for use by the Integrated Risk Information System (IRIS) program.

EPA Oral Reference Dose (Draft)

In 2023, the EPA's Integrated Risk Information System (IRIS) derived a draft oral reference dose of 2×10^{-10} milligrams of PFHxS per kilogram bodyweight per day (mg/kg-d).[12]

To establish the oral reference dose, the EPA selected studies by Budtz-Jørgensen et al. and Grandjean et al. as the critical studies.[13, 14] In these studies, the researchers observed a dose-dependent association between PFHxS serum levels and tetanus and diphtheria antibody concentrations in children. From these studies, the EPA used the benchmark serum dose to derive the draft oral reference dose (Equation 3).

Equation 3: $$\text{Reference Dose (Draft)} = \frac{\text{Point of Departure - Human Equivalent Dose}}{\text{Total Uncertainty Factor}}$$

Where:

Point of Departure- Human Equivalent Dose =

$$\text{Internal Point of Departure} \times \text{Clearance Rate}$$

Point of Departure – Internal ($POD_{Internal}$) = 2.82×10^{-4} mg/L PFHxS in serum

EPA used the benchmark dose at half standard deviation ($BMD_{1/2SD}$). They selected the half standard deviation dose because it provides an extra measure of protection over the full standard deviation dose.

They determined this measure of safety was necessary due to the potential severity of tetanus and diphtheria infections, the life stages evaluated, and the lack of an established minimal biologically significant response level for impacts to antibody response.

Clearance Rate = 4.1×10^{-5} L/kg-d

Estimated average clearance values of PFHxS for adults.

Total Uncertainty Factor = Intraspecies x Database

The EPA used a total uncertainty factor of 30.

They selected an *intraspecies uncertainty factor* (UF_H) of 10 this to account for interindividual differences in human susceptibility.
They selected a *database uncertainty factor* (UF_D) of 3 to account for deficiencies in the toxicity evidence base.

Units: mg/L = milligram of PFHxS per liter of liquid (blood or water)
L/kg-d = liter of blood per kilogram body weight per day

Oncogenic Potential

Wisconsin Stat. ch. 160, requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard.[8] If we determine that a substance is carcinogenic and there is no federal number or ADI from the EPA, then we must set the standard at a level that would result in a cancer risk equivalent to one case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than one in 1,000,000.

To evaluate the oncogenic potential of a substance, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of that substance. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

When establishing the MCL, EPA stated that they had not yet completed a final evaluation and classification of the carcinogenicity of PFHxS.[2] In their draft IRIS review of PFHxS, the EPA concluded that there was inadequate information to assess carcinogenic potential for PFHxS by both oral and inhalation routes of exposure.[12]

The IARC has not evaluated the carcinogenicity of PFHxS.[15]

EPA Cancer Slope Factor

Due to the lack of adequate carcinogenicity data, the EPA has not established a cancer slope factor for PFHxS.[2, 12]

Additional Technical Information

Wisconsin Stat. ch. 160, allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.[8]

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PFHxS, we searched for any guidance values that had been published since DHS completed the literature review for PFHxS in August 2020 as part of the Cycle 11 Groundwater Standards request. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Reference Level

In 2021, the ATSDR released their final Toxicological Profile for Perfluoroalkyls.[1] In this Profile, they established an intermediate oral minimum risk level of 2 x 10^{-5} mg/kg-d for PFHxS.[b]

For the critical study, ATSDR selected a 2009 toxicity study in rats by Butenhoff et al.[16] In this study, male and female adult rats were exposed to different concentrations of PFHxS (0, 0.3, 1, 3, and 10 mg/kg-d) prior to and during mating, pregnancy, and lactation through gavage. The researchers found that PFHxS reduced serum total cholesterol at all doses, increased liver-to-body weight and liver-to-brain weight ratios, and induced centrilobular hepatocellular hypertrophy (increase in liver cell size) and hyperplasia of thyroid follicular cells (increase in number of thyroid cells) at the highest doses.

For the toxicity value, ATSDR selected a No Observable Adverse Effect Level (NOAEL) of 1 mg/kg-d based on the thyroid cell damage observed in parental males.[1] They established the MRL using a human equivalent dose (HED), a total uncertainty factor, and a modifying factor (Equation 4).

Equation 4:
$$\text{Minimum Risk Level} = \frac{\text{Human Equivalent Dose}}{\text{Total Uncertainty Factor x Modifying Factor}}$$

Where: Human Equivalent Dose = 0.0047 mg/kg-d
Estimated from measured serum concentrations in animals using the trapezoid rule (described in more detail **in Appendix B**).

Total Uncertainty Factor = Interspecies x Intraspecies
ATSDR used a total uncertainty factor of 30.
They used an *interspecies uncertainty factor* (UF_S) of 3 to account for the extrapolation of data from animals to humans with dosimetric adjustments.
They used an *intraspecies uncertainty factor* (UF_H) of 10 to account for the interindividual differences in human susceptibility.
Modifying Factor (MF) = 10
ATSDR also added a modifying factor of 10 to account for database limitations.

Units: mg/kg-d = milligram of PFHxS per kilogram body weight per day
L/kg-d = liter of blood per kilogram body weight per day

Literature Search

To ensure that Wisconsin's public health groundwater standards are established based on the best available information, DHS searches for relevant health studies published after the last literature review completed for a health value from the EPA.[c] We used the Web of Science and PubMed databases to look for studies that related to toxicity, effects on a disease state, and the key health effects of genotoxicity, carcinogenicity, teratogenicity, and interactivity for use in establishing the appropriate preventive action limit.

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b The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not establish a chronic oral MRL for PFHxS because they did not identify chronic duration studies and their policy is to not extrapolate across exposure durations.

c The last literature search completed by EPA was in April 2021 by the Integrated Risk Information System program in their work to establish a draft oral refence dose for PFHxS.[15]

We excluded studies that did not meet the Population, Exposure, Comparator, and Outcome (PECO) criteria described in **Table A-1**. After applying these exclusion criteria, we located three key toxicity studies (**Table A-2**) and 98 key epidemiological studies (**Supplemental Table**).

Critical Toxicology Studies

To be considered a critical toxicity study, the study must have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have the appropriate toxicity and pharmacokinetic information necessary to establish an ADI (i.e., identifiable toxicity value, measured serum concentrations, reported half-life).

To compare between results between the critical studies, we calculated a candidate acceptable daily intake (ADI) for each study/effect. We used ATSDR's approach of calculating a human equivalent dose from the measured serum levels using the trapezoid rule to account for differences in the half-life of PFHxS between people and research animals (years compared to days). **Appendix B** has more details on the methodology of this approach.

To obtain the ADI, we then divided the human equivalent dose by the total uncertainty factor – a variable that is used to account the different sources of scientific uncertainty in a research study. In keeping with EPA, we did not use studies that had significant uncertainty as the basis for the recommended enforcement.[17, d] Our *Setting Groundwater Standards to Protect Public Health Guide* has additional information on how an ADI is established.[18]

One of the key toxicity studies meet the critical toxicity study criteria (**Table A-2**).

Critical Epidemiological Studies

To be considered a critical epidemiology study, the study must contain dose-response data in a format that can be used to establish an acceptable daily intake (i.e., established benchmark dose level) or the study must evaluate the impact of exposure at various concentrations of the substance in drinking water.

None of the key epidemiological studies met these criteria (**Supplemental Table**).

Discussion

We identified one critical toxicity study in this literature review. Zhang et al., 2024 evaluated the effects of PFHxS on offspring of mice exposed during pregnancy. They found that the higher dose of PFHxS caused offspring to have lower weight and body length. We calculated a candidate ADI of 1×10^{-6} mg/kg-d – which is consistent with value used by EPA to establish the MCLG for PFHxS.

Key Health Studies

d DHS considers a study to have significant uncertainty if the total uncertainty factors is greater than 3,000.

Wisconsin Stat. ch. 160, states that DHS must recommend a preventive action limit of 10% of the enforcement standard for substances that have carcinogenic, mutagenic, teratogenic, or interactive effects.[8] To recommend the appropriate preventive action limit, we reviewed the available scientific information for evidence of the ability for PFHxS to cause these key health effects.

Key Health Effects for Establishing the Preventive Action Limit	
Carcinogenic:	Evidence indicates that the substance can produce or incite cancer.
Mutagenic:	Evidence indicates that the substance can alter or damage DNA.
Teratogenic:	Evidence indicates that the substance can cause structural defects in unborn babies.
Interactive:	Evidence indicates that the substance can increase the toxicity of other substances or that the substance's toxicity can be increased by the presence of other substances.

Carcinogenicity

Available information on the carcinogenic potential of PFHxS is limited. The ATSDR identified four epidemiology studies examining the association between PFHxS and cancer risk.[1] They found that there no consistent associations for breast cancer risk for PFHxS and did not find any associations between PFHxS and prostate cancer risk. However, associations were found for PFHxS among men with a first-degree relative with prostate cancer.

In establishing the draft oral reference dose, EPA reviewed eight additional studies.[12] They determined that five of these were uninformative and the remaining three studies had low confidence due to deficiencies in participant selection or outcome ascertainment or potential confounding by other PFAS exposures. To date, there have been no studies in research animals examining the effect of PFHxS on cancer outcomes.

In our literature search, we identified a few additional epidemiology studies evaluating the association of PFHxS exposure and cancer risk.[19, 20] In one case-control study, Cirello et al. observed a correlation between PFHxS exposure and thyroid cancer.[19] In another case-cohort study, Winquist et al. observed a positive association between PFHxS concentrations and chronic lymphocytic leukemia/small lymphocytic lymphoma in men.[20]

Mutagenicity

During their reviews, ATSDR and EPA did not identify any studies examining the mutagenic impacts of PFHxS.[1, 2, 12] In our literature search, we identified a study in human liver cells by Ojo et al. In this study, the researchers found that PFHxS caused a moderate, but statistically significant, increase in cellular DNA damage.[21]

Teratogenicity

ATSDR and EPA identified three epidemiology studies that evaluated the association between PFHxS exposure and risk of birth defects.[1, 12, 22-24] However, the study that saw evidence of associations EPA considered a low confidence study due to deficiencies in participant selection, outcome ascertainment, exposure sensitivity, and possible confounding.[12, 22] In our literature search, we did not locate any additional studies examining the teratogenic effects of PFHxS.

Interactivity

The EPA established the hazard index MCL on the based that co-exposure to mixtures of PFAS can produces dose-additive effects.[2, 25] These mixtures included PFHxS. In establishing this approach, they also noted that data show that many PFAS, including PFHxS, cause health effects through the same processes. – for instance by affecting thyroid hormone signaling or impacting immune and liver function.[2, 25] In our literature search, we found numerous epidemiological studies that observed similar effects with PFAS mixtures containing PFHxS.[26-39]

Standard Selection

DHS recommends an enforcement standard of 10 ng/L for PFHxS.

State statute requires that DHS recommend a federal number (such as a maximum contaminant level, health advisory, drinking water concentration based on cancer risk) if one is available and there is no significant technical information to indicate that a different value is more appropriate.

Basis for Enforcement Standard

- ☒ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

The EPA's maximum contaminant level (MCL) for PFHxS was established in April 2024 with their last scientific review completed in April 2021. In our review of toxicological and epidemiological information published since this time, we did not identify significant findings indicating that a value other than the MCL should be used to establish the enforcement standard.

DHS recommends a preventive action limit of 1 ng/L for PFHxS.

DHS recommends that the preventive action limit for PFHxS be set at 10% of the enforcement standard because studies have shown that PFHxS can cause interactive effects.

Prepared by Sarah Yang, PhD with assistance from Becky Bowen, MPH, MS

Wisconsin Department of Health Services

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Appendix A: Literature Review Details

Table A-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria for PFHxS Study Evaluation

Element	Toxicological Inclusion Criteria	Epidemiological Inclusion Criteria
Population:	Non-human mammalian animal species (whole organism) of any life-stage (including preconception, in utero, lactation, peripubertal, and adult stages).	Any population and life-stage (occupational or general population, including children and other sensitive populations).
Exposure:	Any exposure to PFHxS only via oral routes for at least 28 days*	Any exposure to PFHxS via oral routes.
Comparator:	A concurrent control group exposed to vehicle-only treatment or untreated control.	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of PFHxS or exposure to PFHxS for shorter periods of time.
Outcome:	All health outcomes	All health outcomes.

*Exceptions are studies that are conducted during reproduction and/or development.

This literature search was conducted in the National Institutes of Health's *PubMed* resource and Clarivate Analytics' *Web of Science* resource. We used the following search terms in the literature review:

Title/abstract: PFHxS or "perfluorohexane sulfonate" and the synonyms listed in Chemical Properties table
Subject area: toxicology, public environmental occupational health (Web of Science)
MeOH search terms: toxicology, epidemiology, public health (PubMed)
Language: English

Table A-2. PFHxS Key/Critical Toxicity Studies

Reference	Exposure	Key Findings	Critical Toxicity Criteria	Relevant Toxicity Data	Uncertainty Factors[i]	Candidate ADI
Yao et al., 2023 ([40])	Mice were exposed to 0, 0.03, or 0.3 mg/kg-d PFHxS through gavage from GD 7 to 18.	PFHxS crossed the placental barrier reaching the fetus in a dose-dependent manner. Dams showed placenta impairment and disruption of placental lipid homeostasis.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 0.03 mg/kg-d	N/A	N/A
Zhang et al., 2023 ([41])	Mice were exposed to 0, 0.03, or 0.3 mg/kg-d PFHxS through gavage from GD 7 to 17.	PFOA caused smaller weight and body length in fetuses ($p < 0.01$). Dose-dependent PFHxS transfer through placental barrier. Exposed mice had placental dysplasia. Differences in key genes indicated that PFHxS exposure during pregnancy led to impairment of placental amino acid transportation.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ✓ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: 0.03 LOAEL: 0.3 mg/kg-d HED: $1x10^{-5}$ mg/kg-d*	Interspecies: 3 Intraspecies: 10 Duration: 1 Endpoint: 1 Database: 3 Total: 100	1×10^{-6} mg/kg-d[ii]
Zhao et al., 2024 ([42])	Male mice were exposed to 0 or 800 µg/L PFHxS in drinking water for six weeks.	PFHxS exposure changed the composition of the mice gut microbiota and decreased the level of several short-chain fatty acids in the pancreas.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ☒ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 800 µg/L	N/A	N/A

GD = gestational day; HED = human equivalent dose

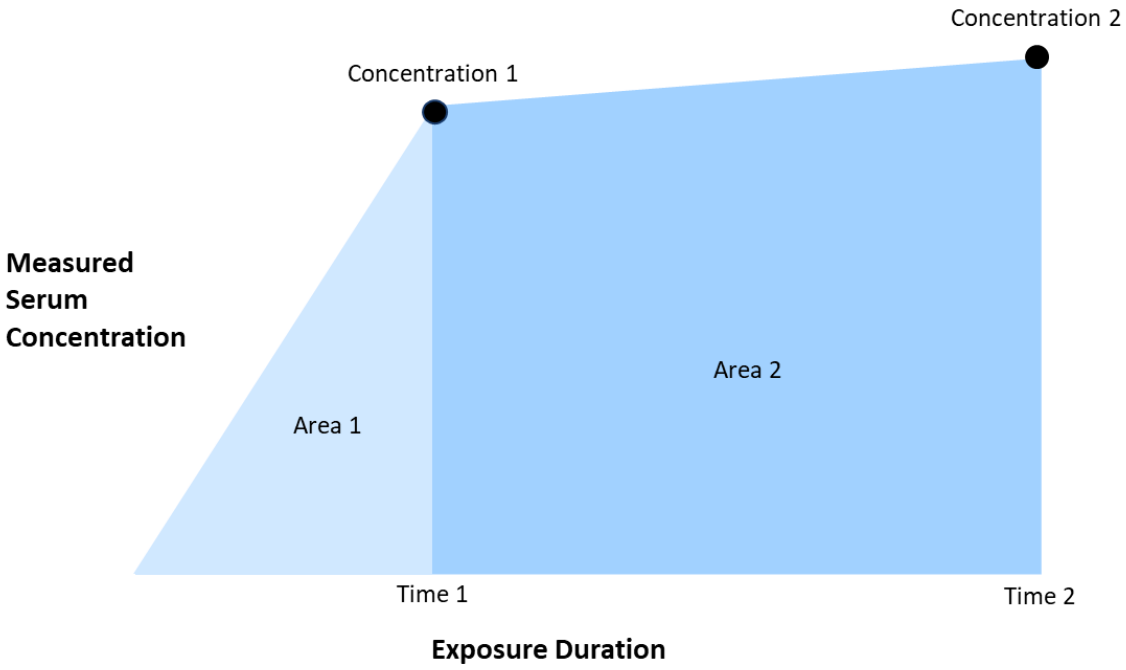
i. More information on how DHS selects uncertainty factors is available in the *Setting Groundwater Standards to Protect Public Health* guide.[18]

ii. More specific details on the calculation of this value are available in the **Supplemental Table.**

Appendix B. Calculation of Human Equivalent Dose

To calculate the human equivalent dose for PFHxS, we followed a three-step process.

1. We first calculated the area under the curve at the selected toxicity value using the trapezoid rule.



In this mathematical approach, the area under the curve is divided into one or more trapezoids and area of each trapezoid is calculated (Equation B-1).

Equation B-1 $$\text{Area} = \frac{h}{2}(p+q)$$

Where:

h = The difference in time between the data points.
q = Measured serum concentration at first time point
p = Measured serum concentration at second time point

The areas of all of the trapezoids are summed to give the area under the curve (Equation B-2).

Equation B-2 $$\text{AUC} = \text{Area}_1 + \text{Area}_2 + \ldots + \text{Area}_n$$

2. We then calculated the time-weight average serum concentration as a surrogate for the steady-state serum concentration (Equation B-3).

Equation B-3 $$\text{TWA} = \frac{\text{AUC}}{\text{ED}}$$

Where:

AUC = The difference in time between the data points.
ED = Exposure duration (days)

3. Finally, we calculated the human equivalent dose (HED) by accounting for the long half-life in people.

$$HED = \frac{TWA \times \frac{\ln 2}{t_{1/2}} \times V_d}{AF}$$

Where:

$t_{1/2}$ = Half-life – measure of measure of a substance's elimination rate.
ATSDR used a value of 3,100 days from data in adults.

V_d = Volume of distribution - theoretical volume needed to contain the amount of the substance administered at the measured serum concentration.
ATSDR used a value of 0.2 L/kg based on studies in nonhuman primates.

AF = Gastrointestinal absorption fraction - measure how much of the chemical is available to cause harm within the body.
ATSDR used a value of 1 based on studies in rodents and non-human primates.

More information on these values is available in ATSDR's *Toxicological Profile for Perfluoroalkyls* – Appendix A.

HFPO-DA | 2024

Substance Overview

Hexafluoropropylene oxide dimer acid (HFPO-DA) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS).[1-4a] HFPO-DA has a branched-chain structure and was created to replace perfluorooctanoic acid (PFOA).[1-4] As such, many products that previously contained PFOA may now contain HFPO-DA, such as carpets, fabrics, non-stick packaging, and some fire-fighting foams.[1-4]

Recommendations

DHS recommends a Public Health Enforcement Standard of 10 nanograms per liter (ng/L) for HFPO-DA. The recommended standard is based on the individual maximum contaminant level (MCL) for HFPO-DA established by the United States Environmental Protection Agency (EPA) in 2024. DHS recommends that the Public Health Preventive Action Limit for HFPO-DA be set at 10% of the enforcement standard because HFPO-DA has been shown to cause carcinogenic and interactive effects.

Recommended Standards	
Enforcement Standard:	10 ng/L
Preventive Action Limit:	1 ng/L

Health Effects

Studies in research animals indicate that HFPO-DA exposure may affect the liver and blood, impact development, and affect the immune system.[1-4]

Exposure Routes

People can be exposed to HFPO-DA by drinking contaminated water, swallowing contaminated soil, eating food that was packaged in material that contains HFPO-DA, consuming fish from contaminated waters, and breathing in or swallowing dust that contains HFPO-DA.[1-4] Additionally, babies born to mothers exposed to HFPO-DA can be exposed to HFPO-DA during pregnancy and breastfeeding.[1-4]

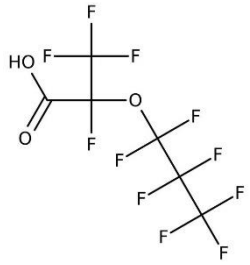
Current Standards

Wisconsin does not currently have NR140 Groundwater Quality Public Health Standards for HFPO-DA.[5]

In 2020, DHS recommended an enforcement standard of 300 nanograms per liter (ng/L) for HFPO-DA. The recommended standard was based on a study in research animals that found that HFPO-DA caused liver damage. We also recommended a preventive action limit of 30 ng/L - 10% of the enforcement standard – because HFPO-DA has been shown to cause carcinogenic and mutagenic effects in research animals and cell culture studies. These standards, however, were not adopted in rule.[6]

[a] HFPO-DA is also referred to as GenX™. However, GenX™ is a processing aid technology developed to make fluoropolymers without PFOA. GenX chemicals include other PFAS than just HFPO-DA.

Chemical Profile

	HFPO-DA
Structure:	
CAS Number:	13252-13-6
Formula:	$C_6HF_{11}O_3$
Molar Mass:	330.05 g/mol
Synonyms:	2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy)propanoic acid Perfluoro-2-methyl-3-oxahexanoic acid Hexafluoropropylene oxide dimer acid Perfluoro(2-methyl-3-oxahexanoic)acid 2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy)propionic acid Perfluoro-2-propoxypropanoic acid

This information was obtained from the PubChem database.[7]

Standards Development

The process for developing groundwater standards is specified in Wisconsin Stat. ch. 160.[8] To develop recommended public health groundwater standards, we (DHS) gather relevant scientific information, select the appropriate standard based on statutory requirements, and document these findings.

Available Scientific Information for HFPO-DA	
Federal Numbers	
Maximum Contaminant Level (Individual):	No
Maximum Contaminant Level (Hazard Index):	**Yes**
Health Advisory:	**Yes**
Drinking Water Concentration (Cancer Risk):	No
State Drinking Water Standard	
NR 809 Maximum Contaminant Level:	No
Acceptable Daily Intake	
EPA Human Health Toxicity Value:	**Yes**
Oncogenic Potential	
EPA Cancer Slope Factor:	No
Guidance Values	
ATSDR Chronic Oral Minimum Risk Level:	No
Technical Information:	
Critical toxicity/epidemiology studies identified?	No

Federal Numbers

Wisconsin Stat. ch. 160, requires that DHS use the most recent federal number as the recommended enforcement standard.[8] This requirement does not apply if a federal number does not exist or there is significant technical information that was not considered when the federal number was established and this information indicates a different number should be used to set the standard.

Maximum Contaminant Level (individual)

In April 2024, the EPA established an individual MCL for HFPO-DA of 10 nanograms per liter (ng/L).

The maximum contaminant level (MCL) is the highest level of a substance that is allowed in drinking water served by public water systems as defined by the Safe Drinking Water Act.[9] To establish an MCL, the United States Environmental Protection Agency (EPA) first derives a maximum contaminant level goal (MCLG).[10] The MCLG is the level of a substance at which health effects are not expected to occur allowing for an adequate margin of safety.[10]

The EPA set the MCL for HFPO-DA equal to its MCLG. The EPA established the MCLG for HFPO-DA using their chronic human health toxicity value (Equation 1).[3]

Equation 1:
$$\text{MCLG} = \frac{\text{Health Based Water Concentration}}{\text{Drinking water Intake}_{\text{BWI}}} \text{ x Relative Source Contribution}$$

Where: Health Based Water Concentration = 3 x 10^{-6} mg/kg-d
EPA used the chronic human health toxicity value that they established for HFPO-DA in 2021 (see *Acceptable Daily Intake* section for more details).
Daily Water Intake (Body Weight Adjusted) = 0.0469 L/kg/day
EPA used the 90th percentile direct and indirect consumption of community water value for lactating people – consumer-only 2-day average.
They selected this value because it is protective of people who are pregnant and people who are breastfeeding.
Relative Source Contribution = 0.2
EPA used the default value; their literature search found that available information did not allow for the quantitative characterization of the relative levels of exposure among these different sources.

Maximum Contaminant Level (Hazard Index)

The EPA also established a Hazard Index Maximum Contaminant Level which includes HPFO-DA.[2, 11] The EPA's Hazard Index MCL is set at 1 and applies to any mixture that contains two or more of PFNA, PFHxS, PFBS, and HFPO-DA.[2, 11] The Hazard Index is made up of a sum of fractions, and each fraction compares the level of each PFAS measured in the water to its health-based water concentration– which is either the individual MCL or the health advisory in the case of PFBS (Equation 2).

Equation 2:
$$\text{Hazard Index} = \frac{\textbf{HFPO-DA Level}}{\textbf{HFPO-DA MCLG}} + \frac{\text{PFBS Level}}{\text{PFBS HA}} + \frac{\text{PFNA Level}}{\text{PFNA MCLG}} + \frac{\text{PFHxS Level}}{\text{PFHxS MCLG}}$$

Where: The "Level" is the concentration of the PFAS detected in public drinking water.
PFBS HA = 2000 ng/L
PFNA MCLG = 10 ng/L
PFHxS MCLG = 10 ng/L

PFBS = perfluorobutanesulfonic acid; PFNA = perfluorononanoic acid; PFHxS = perfluorohexanesulfonic acid
MCLG = Maximum contaminant level goal; HA = drinking water health advisory

Health Advisory

In 2022, EPA established a lifetime health advisory of 2,000 nanograms per liter (ng/L) for HFPO-DA.[4] The EPA established this health advisory using their chronic human health toxicity value for HFPO-DA (Equation 1).

Equation 1:

$$\text{Health Advisory} = \frac{\text{Human Health Toxicity Value}}{\text{Drinking water Intake}_{\text{BWI}}} \text{ x Relative Source Contribution}$$

Where: Human Health Toxicity Value = 3 x 10^{-6} mg/kg-d

EPA used the human health toxicity value that they established for HFPO-DA in 2021 (see *Acceptable Daily Intake* section for more details).

Daily Water Intake (Body Weight Adjusted) = 0.0469 L/kg/day

EPA used the 90th percentile direct and indirect consumption of community water value for lactating people – consumer-only 2-day average.

They selected this value because it is protective of people who are pregnant and people who are breastfeeding.

Relative Source Contribution = 0.2

EPA used the default value; their literature search found that available information did not allow for the quantitative characterization of the relative levels of exposure among these different sources.

Drinking Water Concentration (Cancer Risk)

In establishing the health advisory for HFPO-DA, EPA determined that there were not enough data to establish drinking water concentrations based on cancer risk.

State Drinking Water Standard

Wisconsin Stat. ch. 160, requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a drinking water standard for HFPO-DA.

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, Ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation.[8] Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. ADIs are sometimes termed oral reference doses by EPA. EPA establishes these ADIs to develop a drinking water health advisory, conduct a human health risk assessment for pesticides, or for use by the Integrated Risk Information System (IRIS) program.

EPA Human Health Toxicity Value

In 2021, EPA's Office of Water established a chronic human health toxicity value of 3 x 10^{-6} mg/kg-d for HFPO-DA.

To establish this value, EPA selected a reproductive/developmental toxicity study conducted in mice by Dupont as the critical study.[12] In this study, liver effects were observed at several doses. EPA used benchmark dose modeling and allometric scaling to establish toxicity values for deriving the human health toxicity value (Equation 3).[13, b]

Equation 3: $$\text{Human Health Toxicity Value} = \frac{\text{Human Equivalent Dose}}{\text{Total Uncertainty Factor}}$$

Where: Human Equivalent Dose = Point of Departure x Dose Adjustment Factor

Point of Departure = 0.095 mg/kg-d

EPA used benchmark dose modeling to obtain the point of departure. They identified the $BMDL_{10}$ - lower bound on the benchmark dose level corresponding to the 95% lower confidence limit for a 10% response level – as the critical endpoint.

$$\text{Dose Adjustment Factor} = \frac{\text{Animal Body}^{3/4}}{\text{Human Body}^{3/4}}$$

Dose Adjustment Factor = 0.14

EPA determined that allometric scaled based on body weight was appropriate because life stage-specific BW data from the pregnant or lactating dams was available and half-life data on HFPO-DA is limited.

Animal Body Weight = 0.0349 kg

EPA used the mean body weight of the original female control animals from the last day of the study.

Human Body Weight = 80 kg

EPA used the default body weight for adults more than 21 years of age from their Exposure Factors Handbook.

Total Uncertainty Factor = Interspecies x Intraspecies x Duration x Database

Total Uncertainty Factor = 3000

EPA used an *interspecies uncertainty factor* of 10 this to account for differences between animals and humans.

EPA used an *intraspecies uncertainty factor* of 3 this to account for interindividual differences in human susceptibility.

EPA used a *duration uncertainty factor* of 10 this to account for extrapolating from a subchronic to chronic exposure duration.

EPA used a *database uncertainty factor* of 10 to account for deficiencies in the toxicity evidence base.

Oncogenic Potential

Wisconsin Stat. ch. 160, requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard.[8] If we determine that a substance is carcinogenic and there is no federal number or ADI from the EPA, then we must set the standard at a

b EPA uses allometric scaling to extrapolate dosing across species. it is generally done by adjusting the relevant measure of dose by a ratio of body weights raised to a power.

level that would result in a cancer risk equivalent to one case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than one in 1,000,000.

To evaluate the oncogenic potential of a substance, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of that substance. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

In establishing their health advisory, EPA determined that there is suggestive evidence of carcinogenic potential from oral exposure to GenX chemicals (HFDO-DA) in humans.[4] This determination is based on data from a chronic study in rats.

The IARC has not evaluated the carcinogenicity of HFDO-DA.[14]

EPA Cancer Slope Factor

Because carcinogenicity data are limited, the EPA has not established a cancer slope factor for HFPO-DA.[3, 4]

Additional Technical Information

Wisconsin Stat. ch. 160, allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.[8] To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For HFPO-DA, we searched for any guidance values that had been published since DHS completed the literature review for HFPO-DA in September 2020 as part of the Cycle 11 Groundwater Standards request. We did not find any relevance guidance values.

Literature Search

To ensure that Wisconsin's public health groundwater standards are established based on the best available information, DHS searches for relevant health studies published after the last literature review completed for a health value from the EPA.[c] We used the Web of Science and PubMed databases to look for studies that related to toxicity, effects on a disease state, and the key health effects of genotoxicity, carcinogenicity, teratogenicity, and interactivity for use in establishing the appropriate preventive action limit.

c The last literature search completed by EPA was in April 2021 by the Integrated Risk Information System program in their work to establish a draft oral refence dose for HFPO-DA.

Approximately 100 studies were returned by the search engines. We excluded studies that did not meet the Population, Exposure, Comparator, and Outcome (PECO) criteria described in **Table A-1**. After applying these exclusion criteria, we located three key toxicity studies **(Table A-2)** and four key epidemiological studies **(Supplemental Table**).

Critical Toxicology Studies

To be considered a critical toxicity study, the study must have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have the appropriate toxicity and pharmacokinetic information necessary to establish an ADI (i.e., identifiable toxicity value, measured serum concentrations, reported half-life).

To compare between results between the critical studies, we calculated a candidate acceptable daily intake (ADI) for each study/effect. We used ATSDR's approach of calculating a human equivalent dose from the measured serum levels using the trapezoid rule to account for differences in the half-life of HFPO-DA between people and research animals (years compared to days). **Appendix B** has more details on the methodology of this approach.

To obtain the ADI, we then divided the human equivalent dose by the total uncertainty factor – a variable that is used to account the different sources of scientific uncertainty in a research study. In keeping with EPA practices, we did not use studies that had significant uncertainty as the basis for the recommended enforcement.[13d] Our *Setting Groundwater Standards to Protect Public Health Guide* has additional information on how an ADI is established.[15]

Two of key toxicity studies meet these critical toxicity study criteria (**Table A-1**).

Critical Epidemiological Studies

To be considered a critical epidemiology paper, the study must contain dose-response data in a format that can be used to establish an acceptable daily intake (i.e., established benchmark dose level) or the study must evaluate the impact of exposure at various concentrations of the substance in drinking water.

None of the key epidemiological studies met these criteria (**Supplemental Table**).

Discussion

We located two critical toxicity studies in this literature review. Cope et al., 2022 evaluated the effect of HFPO-DA on offspring after exposing pregnant mice for 6 or 18 weeks while feeding them a low- or high-fat diet.[16] They found that the highest dose caused males fed the low-fat diet to have increased weight gain, fat mass, liver cell changes, and insulin sensitivity. We calculated a candidate ADI of 1×10^{-5} mg/kg-d – which is an order of magnitude higher than the human health toxicity value used by EPA to establish the MCLG for HFPO-DA.

On the other hand, the study by Shi et al., 2024 evaluated the effects of HFPO-DA on male mice during and after 98 days of exposure and found effects at lower levels.[17] They found that HFPO-DA caused a

d DHS considers a study to have significant uncertainty if the total uncertainty factors is greater than 3,000.

dose−dependent increase in collagen fibers in the liver and a dose-dependent decrease in superoxide dismutase levels. We calculated a candidate ADI of 2x 10^{-8} mg/kg-d. This value is lower than the toxicity value used by EPA to establish the MCLG for HFPO-DA by several orders of magnitude. However, this may be due to an increase in the endpoint uncertainty factor.

The findings of both studies are in keeping with existing toxicological and epidemiological data on the effects of HFPO-DA and are supportive of EPA's existing health thresholds – including the MCL.

Key Health Effects for Establishing the Preventive Action Limit	
Carcinogenic:	Evidence indicates that the substance can produce or incite cancer.
Mutagenic:	Evidence indicates that the substance can alter or damage DNA.
Teratogenic:	Evidence indicates that the substance can cause structural defects in unborn babies.
Interactive:	Evidence indicates that the substance can increase the toxicity of other substances or that the substance's toxicity can be increased by the presence of other substances.

Key Health Studies

Wisconsin Stat. ch. 160, states that DHS must recommend a preventive action limit of 10% of the enforcement standard for substances that have carcinogenic, mutagenic, teratogenic, or interactive effects.[8] To recommend the appropriate preventive action limit, we reviewed the available scientific information for evidence of the ability for HFPO-DA to cause these key health effects.

Carcinogenicity

As noted above, EPA has determined that there is suggestive evidence of carcinogenic potential from oral exposure to GenX chemicals (HFDO-DA) in humans.[3, 4] This determination is based on the results from a study completed by DuPont in 2013 in which long-term exposure to high levels of HFPO-DA caused several carcinogenic effects (liver tumors, pancreas adenomas and carcinomas, and testicular cell adenoma) in rats.[12]

Mutagenicity

During their reviews, EPA and ATSDR did not identify any evidence of mutagenic effects in people, research animals, or cell culture studies.[1-4] In our literature search, we did not locate any additional studies examining the mutagenic potential of HPFO-DA.

Teratogenicity

While evaluating data for their health advisory, EPA noted HFPO-DA exposure did not cause any structural defects in research animals.[3, 4] In our literature search, we found one study that indicated that HFPO-DA can delay skeletal development in research animals; however, this delay did not result in teratogenic effects.[18]

Interactivity

The EPA established the hazard index MCL on the basis that co-exposure to mixtures of PFAS can produces dose-additive effects.[2, 19] These mixtures included HFPO-DA. In establishing this approach, they

also noted that data show that many PFAS, including HFPO-DA, cause health effects through the same processes – for instance, by affecting thyroid hormone signaling or impacting immune and liver function.[2, 19] We found similar evidence in our literature search.[20, 21]

Standard Selection

DHS recommends an enforcement standard of 10 ng/L for HFPO-DA.

State statute requires that DHS recommend a federal number (such as a maximum contaminant level, health advisory, drinking water concentration based on cancer risk) if one is available and there is no significant technical information to indicate that a different value is more appropriate.

Basis for Enforcement Standard

- ☒ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

The EPA's maximum contaminant level (MCL) for HPFO-DA was established in April 2024 with their last scientific review completed in April 2021. In our review of toxicological and epidemiological information published since this time, we did not identify significant findings indicating that a value other than the MCL should be used to establish the enforcement standard.

DHS recommends a preventive action limit of 1 ng/L for HFPO-DA.

DHS recommends that the preventive action limit for HFPO-DA be set at 10% of the enforcement standard because studies have shown that HFPO-DA can cause carcinogenic and interactive effects. Studies, to date, have not shown that HFDO-DA can cause mutagenic or teratogenic effects.

Prepared by Sarah Yang, PhD with assistance from Becky Bowen, MPH, MS

Wisconsin Department of Health Services

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Appendix A: Literature Review Details

Table A-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria for HFPO-DA Study Evaluation

Element	Toxicological Inclusion Criteria	Epidemiological Inclusion Criteria
Population:	Non-human mammalian animal species (whole organism) of any life-stage (including preconception, in utero, lactation, peripubertal, and adult stages).	Any population and life-stage (occupational or general population, including children and other sensitive populations).
Exposure:	Any exposure to HFPO-DA only via oral routes for at least 28 days*	Any exposure to HFPO-DA via oral routes.
Comparator:	A concurrent control group exposed to vehicle-only treatment or untreated control.	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of HFPO-DA or exposure to HFPO-DA for shorter periods of time.
Outcome:	All health outcomes	All health outcomes.

*Exceptions are studies that are conducted during reproduction and/or development.

This literature search was conducted in the National Institutes of Health's *PubMed* resource and Clarivate Analytics' *Web of Science* resource. We used the following search terms in the literature review:

Title/abstract: HFPO-DA or "hexafluoropropylene oxide dimer acid" and the synonyms listed in Chemical Properties table.
Subject area: toxicology, public environmental occupational health (Web of Science)
MeOH search terms: toxicology, epidemiology, public health (PubMed)
Language: English

Table A-2. HFPO-DA Key/Critical Toxicity Studies

Reference	Exposure	Key Findings	Critical Toxicity Criteria	Relevant Toxicity Data	Uncertainty Factor	Candidate ADI*
Cope et al., 2022[16]	Pregnant mice were exposed to 0, 0.2, 1, or 2 mg/kg-d HFPO-DA via gavage. Offspring were then fed a high or low-fat diet for 6 or 18 weeks.	The highest dose caused males fed the low-fat diet to have increased weight gain, fat mass, liver cell changes, and insulin sensitivity.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ✓ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL (females): 1 mg/kg-d $Half\text{-}Life_{Mice}$: 24 hr $Half\text{-}Life_{Human}$: 81 hr	Interspecies: 3 Intraspecies: 10 Duration: 1 Endpoint: 10 Database: 10 Total: 3,000	1×10^{-5} mg/kg-d
Shi et al., 2024[17]	Male mice were exposed to 0.1, 10, 1000, and 10,000 µg/L GenX in drinking water for 98 days.	HFPO-DA caused a dose−dependent increase in collagen fibers in the liver and a dose-dependent decrease in superoxide dismutase levels.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ✓ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 0.1 µg/L $Body\ Weight_{Mice}$: 0.02 kg $Body\ Weight_{Human}$: 80 kg	Interspecies: 10 Intraspecies: 3 Duration: 1 Endpoint: 10 Database: 10 Total: 3,000	2×10^{-8} mg/kg-d
Wang et al., 2024[18]	Male mice were exposed to 0, 2, or 4 mg/kg-d HFPO-DA via oral gavage for 28 days.	HFPO-DA decreased femur and tibia length at both doses. significant reduction in bone density. Also promoted osteoblast senescence and impaired osteogenic capabilities.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: N/A LOAEL: 2 mg/kg-d	Interspecies: 3 Intraspecies: 10 Duration: 10 Endpoint: 10 Database: 10 Total: 30,000	N/A Uncertainty too high for derivation

GD = gestational day; hr = hour

*Candidate ADIs were calculated by dividing the human equivalent dose (HED) by the total uncertainty factor. The HED was obtained by multiplying the applicable toxicity value (NOAEL/LOAEL) by a dose-adjustment factor based on either half-lives or body weights.

PFBS | 2024

Substance Overview

Perfluorobutanesulfonic acid (PFBS) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS).[1-4] PFBS is made up of four carbon-fluorine bonds and a sulfonic acid group.[1-4] Because PFBS contains less than six carbon-fluorine bonds, it is considered a short-chain PFAS. Short-chain PFAS, like PFBS, do not last as long in the body as long-chain PFAS.[1-3]

PFBS has been used as replacement for the longer-chain PFAS perfluorooctanesulfonic acid (PFOS) in products ranging from cleaners to paints to stain repellants.[1-4] PFBS has also been found in floor wax, firefighting foam, and carpeting.[1-4]

Recommendations

DHS recommends a Public Health Enforcement Standard of 2,000 nanograms per liter (ng/L) for PFBS. The recommended standard is based on the lifetime drinking water health advisory established by the United States Environmental Protection Agency (EPA). DHS recommends that the Public Health Preventive Action Limit for PFBS be set at 10% of the enforcement standard because PFBS has been shown to cause interactive effects.

Recommended Standards	
Enforcement Standard:	2,000 ng/L
Preventive Action Limit:	200 ng/L

Health Effects

Studies among research animals indicate that PFBS exposure may affect the thyroid and kidneys and impact development.[1-3]

Exposure Routes

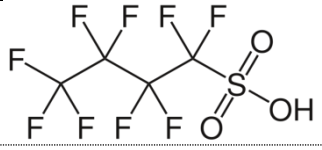
People can be exposed to PFBS by drinking contaminated water, swallowing contaminated soil, eating food that was packaged in material that contains PFBS, consuming fish from contaminated waters, and breathing in or swallowing dust that contains PFBS.[1-3] Additionally, babies born to mothers exposed to PFBS can be exposed to PFBS during pregnancy and breastfeeding.[3]

Current Standards

Wisconsin does not currently have NR140 Groundwater Quality Public Health Standards for PFBS.[5]

In 2020, DHS recommended an enforcement standard of 450 micrograms per liter (µg/L) for PFBS.[6] The recommended standard was based on a study in research animals that found that PFBS exposure increased body weight and caused kidney damage. We also recommended a preventive action limit of 90 µg/L – 20% of the enforcement standard because PFBS had not been shown to cause carcinogenic, mutagenic, teratogenic, or interactive effects in people, research animals, or cell culture studies at the time of the recommendation. These standards, however, were not adopted in rule.[7]

Chemical Profile

	PFBS
Structure:	
CAS Number:	375-73-5
Formula:	$C_4HF_9O_3S$
Molar Mass:	300.09 g/mol
Synonyms:	Nonafluorobutanesulfonic acid Nonafluoro-1-butanesulfonic acid Nonafluorobutane-1-sulfonic acid 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid Perfluorobutane sulfonic acid Perfluoro-1-butanesulfonic Acid Perfluorobutane sulfonate Perfluorobutanesulphonic acid perfluorobutyl sulfonic acid perfluorobutane-1-sulfonic acid

This information was obtained from the PubChem database.[8]

Standards Development

The process for developing groundwater standards is specified in Wis. Stat. ch. 160.[9] To develop recommended public health groundwater standards, we (DHS) gather relevant scientific information, select the appropriate standard based on statutory requirements, and document these findings.

Available Scientific Information for PFBS	
Federal Numbers	
Maximum Contaminant Level (Individual):	No
Maximum Contaminant Level (Hazard Index):	**Yes**
Health Advisory:	**Yes**
Drinking Water Concentration (Cancer Risk):	No
State Drinking Water Standard	
NR 809 Maximum Contaminant Level:	No
Acceptable Daily Intake	
EPA Human Health Toxicity Value:	**Yes**
Oncogenic Potential	
EPA Cancer Slope Factor:	No
Guidance Values	
ATSDR Chronic Oral Minimum Risk Level:	No
Technical Information:	
Critical toxicology or epidemiology studies identified?	**Yes**

Federal Numbers

Wis. Stat. ch. 160, requires that DHS use the most recent federal number as the recommended enforcement standard.[9] This requirement does not apply if a federal number does not exist or there is significant technical information that was not considered when the federal number was established and this information indicates a different number should be used to set the standard.

Maximum Contaminant Level (individual)

The United States Environmental Protection Agency (EPA) has not established an individual maximum contaminant level (MCL) for PFBS.[10, 11, a]

Maximum Contaminant Level (Hazard Index)

The EPA established a hazard index maximum contaminant level for four PFAS, including PFBS.[10, 12] The hazard index is an approach used to account for the risk to exposure to combined and co-occurring levels of these PFAS in drinking water. The EPA's Hazard Index MCL is set at 1 and applies to any mixture that contains two or more of HFPO-DA (GenX), PFBS, PFNA, and PFHxS.

The Hazard Index MCL compares the level of each PFAS measured in the water to its health-based water concentration – which is either the individual MCLG or the health advisory in the case of PFBS (Equation 2).

Equation 2:

$$\text{Hazard Index} = \frac{\text{HFPO-DA Level}}{\text{HFPO-DA MCLG}} + \frac{\textbf{PFBS Level}}{\textbf{PFBS HA}} + \frac{\text{PFNA Level}}{\text{PFNA MCLG}} + \frac{\text{PFHxS Level}}{\text{PFHxS MCLG}}$$

Where: The "Level" is the concentration of the PFAS detected in public drinking water.
HFPO-DA MCLG = 10 ng/L
PFBS HA = 2000 ng/L
PFNA MCLG = 10 ng/L
PFHxS MCLG = 10 ng/L

HFPO-DA = hexafluoropropylene oxide dimer acid (also referred to as GenX); PFNA = perfluorononanoic acid; PFHxS = perfluorohexanesulfonic acid; MCLG = maximum contaminant level goal; HA = drinking water health advisory

Health Advisory

In 2022, EPA established a lifetime health advisory of 2,000 nanograms per liter (ng/L) for PFBS.[2] The EPA established this health advisory using their chronic human health toxicity value for PFBS (Equation 1).

Equation 1:

$$\text{Health Advisory} = \frac{\text{Human Health Toxicity Value}}{\text{Drinking water Intake}_{\text{BWI}}} \text{ x Relative Source Contribution}$$

Where: Human Health Toxicity Value = 3 x 10^{-4} mg/kg-d
EPA used the value that they established in 2021 (see *Acceptable Daily Intake* section for more details).

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a In their *Response to Comments on the National Primary Drinking Water Standards*, the EPA stated that they decided to defer establishing an individual MCL for PFBS until there is more information on the likelihood that PFBS will individually occur in public water systems and at a level of public health concern.[11]

Daily Water Intake (Body Weight Adjusted) = 0.0354 L/kg-d

90th percentile direct and indirect consumption of community water, consumer-only two-day average, women, ages 13 to < 50 years. EPA selected this value because it is protective of people who are of childbearing age.

Relative Source Contribution = 0.2

EPA used the default value; they found that the available information did not allow for the quantitative characterization of the relative levels of exposure among these different sources.

Drinking Water Concentration (Cancer Risk)

In establishing the health advisory, EPA determined that there were not enough carcinogenicity data to establish a drinking water concentration based on a cancer risk level for PFBS.[1, 2]

State Drinking Water Standard

Wis. Stat. ch. 160, requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a drinking water standard for PFBS.[13]

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, Ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation.[9] Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. ADIs are sometimes termed oral reference doses by EPA. EPA establishes these ADIs to develop a drinking water health advisory, conduct a human health risk assessment for pesticides, or for use by the Integrated Risk Information System (IRIS) program.

EPA Human Health Toxicity Value

In 2021, EPA's Office of Research and Development established a chronic human health toxicity value of 3×10^{-4} PFBS per kilogram bodyweight per day (mg/kg-d).[1, 2]

To establish the oral reference dose, the EPA selected a study by Feng et al. as the critical study.[14] In this study, the two highest doses of PFBS caused a statistically significant decrease in thyroid hormone levels on gestational day 20. EPA used benchmark dose modeling to establish toxicity values for deriving the human health toxicity value (Equation 3).[15]

Equation 3:
$$\text{Human Health Toxicity Value} = \frac{\text{Human Equivalent Dose}}{\text{Total Uncertainty Factor}}$$

Where:

$$\text{Human Equivalent Dose} = \text{Point of Departure} \times \frac{\text{Half-Life}_{\text{animal}}}{\text{Half-life}_{\text{Human}}}$$

Point of Departure = 0.095 mg/kg-d

EPA used the benchmark dose at half standard deviation ($BMD_{1/2SD}$.

Half-Life$_{Animal}$ = 4.5 hours

EPA used the terminal serum half-life of combined doses for female mice.

Half-Life$_{Human}$ = 1,050 hours

EPA used the mean serum half-life from combined sexes.

Total Uncertainty Factor = Interspecies x Intraspecies x Database

Total Uncertainty Factor = 300

EPA used an interspecies uncertainty factor of 3 this to account for differences between animals and humans.

EPA used an interspecies uncertainty factor of 10 this to account for interindividual differences in human susceptibility.

EPA used a database uncertainty factor of 10 to account for deficiencies in the toxicity evidence base.

Oncogenic Potential

Wis. Stat. ch. 160, requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard.[9] If we determine that a substance is carcinogenic and there is no federal number or ADI from the EPA, then we must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of a substance, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of that substance. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

In establishing the health advisory, EPA determined that there was inadequate information to assess carcinogenic potential of PFBS by any route of exposure.[1, 2]

The IARC has not evaluated the carcinogenicity of PFBS.[16]

EPA Cancer Slope Factor

Due to the lack of adequate carcinogenicity data, the EPA has not established a cancer slope factor for PFBS.[1, 2]

Additional Technical Information

Wis. Stat. ch. 160, allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PFBS, we searched for any guidance values that had been published since DHS completed the literature review for PFBS in August 2020 as part of the Cycle 11 Groundwater Standards request. We did not find any relevance guidance values.

Literature Search

To ensure that Wisconsin's public health groundwater standards are established based on the best available information, DHS searches for relevant health studies published after the last literature review completed for a health value from the EPA.[b] We used the Web of Science and PubMed databases to look for studies published that related to toxicity, effects on a disease state, and the key health effects of genotoxicity, carcinogenicity, teratogenicity, and interactivity for use in establishing the appropriate preventive action limit.

Approximately 300 studies were returned by the search engines. We excluded studies that did not meet the Population, Exposure, Comparator, and Outcome (PECO) criteria described in **Table A-1**. After applying these exclusion criteria, we located three key toxicity studies (**Table A-2**) and 26 key epidemiological studies (**Supplemental Table**).

Critical Toxicology Studies

To be considered a critical toxicity study, the study must have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have the appropriate toxicity and pharmacokinetic information necessary to establish an ADI (i.e., identifiable toxicity value, measured serum concentrations, reported half-life).

To compare between results between the critical studies, we calculated a candidate acceptable daily intake (ADI) for each study/effect. Because the half-life of PFBS is longer in people than it is in research animals, we used approach of calculating a human equivalent dose using half-live ratios.[1]

To obtain the ADI, we then divided the human equivalent dose by the total uncertainty factor – a variable that is used to account the different sources of scientific uncertainty in a research study. In keeping with EPA practices, we did not use studies that had significant uncertainty as the basis for the recommended enforcement.[17c] Our *Setting Groundwater Standards to Protect Public Health Guide* has additional information on how an ADI is established.[18]

Two of the key toxicity studies meet these criteria (**Table A-1**).

Critical Epidemiological Studies

To be considered a critical epidemiology paper, the study must contain dose-response data in a format that can be used to establish an acceptable daily intake (i.e., established benchmark dose level) or the

b The last literature search completed by EPA was in April 2021 by the Integrated Risk Information System program in their work to establish a draft oral refence dose for PFBS.
c DHS considers a study to have significant uncertainty if the total uncertainty factors is greater than 3,000.

study must evaluate the impact of exposure at various concentrations of the substance in drinking water.

None of the key epidemiology studies meet these criteria (**Supplemental Table**).

Discussion

We identified two critical toxicity studies in this literature review. Yu et al. evaluated the effects of two doses of PFBS on pregnant rats.[19] They found that the higher dose significantly decreased one-hour glucose levels and reduced the area under the curve in the oral glucose tolerance test. We calculated a candidate ADI of 2.7 x 10^{-4} mg/kg-d.

Appiah et al. evaluated the effects of two doses of PFBS on male rats after 11 weeks of exposure.[20] They found that the lower dose of PFBS significantly increased mean liver and body weights, the higher dose significantly decreased the alanine aminotransferase (ALT) enzyme level, and both doses significantly decreased total antioxidant capacity. We calculated a candidate ADI of 2.3 x 10^{-4} mg/kg-d – which is consistent with value used by EPA to establish the MCLG for PFBS.

The findings of both studies are in keeping with existing toxicological and epidemiological data on the effects of PFBS and are supportive of EPA's existing health thresholds including the MCL.

Key Health Studies

Wis. Stat. ch. 160, states that DHS must recommend a preventive action limit of 10% of the enforcement standard for substances that have carcinogenic, mutagenic, teratogenic, or interactive effects.[9] To recommend the appropriate preventive action limit, we reviewed the available scientific information for evidence of the ability for PFBS to cause these key health effects.

Key Health Effects for Establishing the Preventive Action Limit	
Carcinogenic:	Evidence indicates that the substance can produce or incite cancer.
Mutagenic:	Evidence indicates that the substance can alter or damage DNA.
Teratogenic:	Evidence indicates that the substance can cause structural defects in unborn babies.
Interactive:	Evidence indicates that the substance can increase the toxicity of other substances or that the substance's toxicity can be increased by the presence of other substances.

Carcinogenicity

In their reviews, ATSDR and EPA did not find any toxicology or epidemiology studies evaluating the carcinogenicity of PFBS.[1, 3] In our literature search, we found one cell culture study that found that PFBS did not increase breast cell proliferation – a marker of breast cancer risk.[21]

Mutagenicity

In their reviews, ATSDR and EPA did not find any evidence of mutagenic effects in studies among people or in research animals or cell cultures.[1, 3] In our literature search, we did not locate any studies on the mutagenic effects of PFBS.

Teratogenicity

In their reviews, ATSDR and EPA did not find any human studies examining the impact of PFBS exposure on teratogenicity.[1, 3] EPA also reviewed a handful of studies conducted in research animals and noted that PFBS did not impact fetal morphology (i.e., malformations and variations) in any of these studies.[1, 14, 22-24] In our literature search, we did not locate any studies on the teratogenic effects of PFBS.

Interactivity

The EPA established the hazard index MCL on the basis that co-exposure to mixtures of PFAS can produces dose-additive effects.[12, 25] These mixtures included PFBS. In establishing this approach, they also noted that data show that many PFAS, including PFBS, cause health effects through the same processes – for instance by affecting thyroid hormone signaling or impacting immune and liver function.[12, 25] We found similar evidence in our literature search.[26-33]

Standard Selection

DHS recommends an enforcement standard of 2,000 ng/L for PFBS.

State statute requires that DHS recommend a federal number (such as a maximum contaminant level, health advisory, drinking water concentration based on cancer risk) if one is available and there is no significant technical information to indicate that a different value is more appropriate.

Basis for Enforcement Standard

- ☒ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

The EPA's health advisory (MCL) for PFBS was established in 2023 with their last scientific review completed in April 2021. In our review of toxicological and epidemiological information published since this time, we did not identify significant findings indicating that a value other than the MCL should be used to establish the enforcement standard.

DHS recommends a preventive action limit of 200 ng/L for PFBS.

DHS recommends that the preventive action limit for PFBS be set at 10% of the enforcement standard because studies have shown that PFBS can cause interactive effects. Studies, to date, have not shown that PFBS can cause carcinogenic, mutagenic, or teratogenic effects.

Prepared by Sarah Yang, PhD with assistance from Becky Bowen, MPH, MS

Wisconsin Department of Health Services

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Appendix A: Literature Review Details

Table A-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria for PFBS Study Evaluation

Element	Toxicological Inclusion Criteria	Epidemiological Inclusion Criteria
Population:	Non-human mammalian animal species (whole organism) of any life-stage (including preconception, in utero, lactation, peripubertal, and adult stages).	Any population and life-stage (occupational or general population, including children and other sensitive populations).
Exposure:	Any exposure to PFBS only via oral routes for at least 28 days*	Any exposure to PFBS via oral routes.
Comparator:	A concurrent control group exposed to vehicle-only treatment or untreated control.	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of PFBS or exposure to PFBS for shorter periods of time.
Outcome:	All health outcomes	All health outcomes.

*Exceptions are studies that are conducted during reproduction and/or development.

This literature search was conducted in the National Institutes of Health's *PubMed* resource and Clarivate Analytics' *Web of Science* resource. We used the following search terms in the literature review:

Title/abstract: PFBS or "perfluorobutane sulfonate" and the synonyms listed in Chemical Properties table
Subject area: toxicology, public environmental occupational health (Web of Science)
MeOH search terms: toxicology, epidemiology, public health (PubMed)
Language: English

Table A-2. PFBS Key/Critical Toxicity Studies

Reference	Exposure	Key Findings	Critical Toxicity Criteria	Relevant Toxicity Data	Uncertainty Factors	Candidate ADI*
Crute et al., 2023[34]	Female rabbits were exposed to 0, 0.10, or 100 mg/L PFBS* in drinking water for 32 days from preconception through gestation.	The higher dose of PFBS caused changes in blood pressure in dams and decreased crown-rump length in offspring.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ☒ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: 10 mg/L (0.65±0.11 mg/kg-d) LOAEL: 100 mg/L (6.8±1.4 mg/kg-d)	N/A Interspecies: 3 Intraspecies: 10 Duration: 3 Endpoint: 3 Database: 3 Total: 1000	N/A
Yu et al., 2024[19]	Female rats were exposed to 0, 5, or 50 mg/kg-d PFBS through gavage from GD 1 to 20.	The higher dose of PFBS caused a significant decrease in one-hour glucose levels and the area under the curve in the oral glucose tolerance test.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ✓ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: 5 mg/kg-d LOAEL: 50 mg/kg-d Human Half-Life: 1050 hr Rat Half-Life: 5.7 hr (female) HED: 0.027 mg/kg-d	Interspecies: 3 Intraspecies: 10 Duration: 1 Endpoint: 1 Database: 10 Total: 300	2.7×10^{-4} mg/kg-d
Appiah et al., 2024[20]	Male rats were exposed to 0, 50, or 100 ppm (mg/kg-d) PFBS in diet for 11 weeks.	The low dose of PFBS caused a significant increase in mean liver weight and body weight. The high dose caused a significant decrease in ALT level and both doses caused a significant decrease in total antioxidant capacity.	✓ Appropriate duration. ✓ Effects consistent with other studies and relevant to humans. ✓ Evaluated more than one dose. ✓ Toxicity and pharmacokinetic information available for establishing an ADI.	NOAEL: 50 mg/kg-d LOAEL: 100 mg/kg-d Human Half-Life: 1050 hr Rat Half-Life: 4.8 hr HED: 0.23 mg/kg-d	Interspecies: 3 Intraspecies: 10 Duration: 3 Endpoint: 3 Database: 3 Total: 1000	2.3×10^{-4} mg/kg-d

GD = gestational day; hr = hour

*Candidate ADIs were calculated by dividing the human equivalent dose (HED) by the total uncertainty factor. The HED was obtained by multiplying the applicable toxicity value (NOAEL/LOAEL) by the ratio of animal to human half-lives. Half-life data is from Table 8 in EPA's *Human Health Toxicity Values for Perfluorobutane Sulfonic Acid* report.[1]

Supplemental Table S1: Key epidemiological studies identified as during DHS' literature review

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Association between maternal exposure to perfluoroalkyl and polyfluoroalkyl substances and risks of adverse	2021	Development	Various	No	No	N/A	No	**Yes**	No	**Yes**
Association between per and polyfluoroalkyl substances and markers of inflammation and oxidative stress (10.1016/j.envres.2020.110361)	2021	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Associations of exposure to perfluoroalkyl substances individually and in mixtures with persistent infections: Recent findings from NHANES 1999-2016 (10.1016/j.envpol.2021.116619)	2021	Immune	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Environmental exposure to perfluoroalkyl substances in early pregnancy, maternal glucose homeostasis and the risk of gestational diabetes: A prospective cohort study (10.1016/j.envint.2021.106621)	2021	Other	Serum	**Yes**	N/A	**Yes**	No	N/A	N/A	**Yes**
Exposure to perfluoroalkyl substances (PFAS) and dyslipidemia, hypertension and obesity in adolescents. The Fit Futures study (10.1016/j.envres.2021.110740)	2021	Lipid	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Exposure to Perfluoroalkyl Substances and Glucose Homeostasis in Youth (10.1289/EHP9200)	2021	Endocrine	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Perfluoroalkyl substances and immune cell counts in adults from the Mid-Ohio Valley (USA) (10.1016/j.envint.2021.106599)	2021	Immune	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
PFAS Concentrations and Cardiometabolic Traits in Highly Exposed Children and Adolescents (10.3390/ijerph182412881)	2021	Lipid	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Prenatal and postnatal exposure to PFAS and cardiometabolic factors and inflammation status in children from six European cohorts (10.1016/j.envint.2021.106853)	2021	Cardiovascular	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Serum concentrations of per-/polyfluoroalkyl substances and risk of type 2 diabetes: A case-control study (10.1016/j.scitotenv.2021.147476)	2021	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Serum perfluoroalkyl substances in relation to lipid metabolism in Chinese pregnant women (10.1016/j.chemosphere.2020.128566)	2021	Lipid	Serum	**Yes**	N/A	**Yes**	No	N/A	N/A	**Yes**
Association between prenatal exposure to perfluoroalkyl substances and anogenital distance in female neonates (10.1016/j.ecoenv.2022.114130)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	Key PFAS cause signifcant effect?
Association between serum per- and polyfluoroalkyl substances concentrations and common cold among children and adolescents in the United States (10.1016/j.envint.2022.107239)	2022	Immune	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Association of emerging and legacy per- and polyfluoroalkyl substances with unexplained recurrent spontaneous abortion (10.1016/j.ecoenv.2022.113691)	2022	Other	Serum	No	N/A	No	**Yes**	N/A	N/A	**Yes**
Association of maternal perfluoroalkyl substance exposure with postpartum haemorrhage in Guangxi, China (10.1016/j.ecoenv.2022.114078)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Association of single and multiple prefluoroalkyl substances exposure with preterm birth: Results from a Chinese birth cohort study (10.1016/j.chemosphere.2022.135741)	2022	Other	Serum	**Yes**	N/A	**Yes**	No	N/A	N/A	**Yes**
Associations between PFAS occurrence and multimorbidity	2022	Other	)rinking wate	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Associations of prenatal exposure to perfluoroalkyl substances with preterm birth: A family-based birth cohort study (10.1016/j.envres.2022.113803)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Concentrations of tetanus and diphtheria antibodies in vaccinated Greenlandic children aged 7-12 years exposed to marine pollutants, a cross sectional study (10.1016/j.envres.2021.111712)	2022	Immune	Serum	**Yes**	N/A	N/A	No	N/A	N/A	**Yes**
Cross-sectional associations between serum PFASs and inflammatory biomarkers in a population exposed to AFFF-contaminated drinking water (10.1016/j.ijheh.2021.113905)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	No
Drinking Water-Associated PFAS and Fluoroethers and Lipid Outcomes in the GenX Exposure Study (10.1289/EHP11033)	2022	Lipids	Serum	No	N/A	No	No	N/A	N/A	N/A
Early-life exposure to perfluoroalkyl substances in relation to serum adipokines in a longitudinal birth cohort (10.1016/j.envres.2021.111905)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Exposure to per- and polyfluoroalkyl substances as a risk factor for gestational diabetes mellitus through interference with glucose homeostasis (10.1016/j.scitotenv.2022.156561)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	No

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Individual and mixture associations of perfluoroalkyl substances on liver function biomarkers in the Canadian Health Measures Survey (10.1186/s12940-022-00892-6)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Per- and polyfluoroalkyl substance (PFAS) exposure, maternal metabolomic perturbation, and fetal growth in African American women: A meet-in-the-middle approach (10.1016/j.envint.2021.106964)	2022	Development	Serum	**Yes**	N/A	No	No	N/A	N/A	No
Per- and polyfluoroalkyl substances and incident diabetes in midlife women: the Study of Women's Health Across the Nation (SWAN) (10.1007/s00125-022-05695-5)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Per- and Polyfluoroalkyl Substances and Incident Hypertension in Multi-Racial/Ethnic Women: The Study of Women's Health Across the Nation (10.1161/HYPERTENSIONAHA.121.18809)	2022	Cardiovascular	Serum	**Yes**	N/A	No	No	N/A	N/A	No
Per- and polyfluoroalkyl substances in drinking water and hy	2022	Other	Drinking wate	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Perfluoroalkyl substance mixtures and cardio-metabolic outcomes in highly exposed male workers in the Veneto Region: A mixture-based approach (10.1016/j.envres.2022.113225)	2022	Lipid	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
Risk of Cancer in a Community Exposed to Per- and Poly-Fluoroalkyl Substances (10.1177/11786302221076707)	2022	Cancer	Drinking Water, serum	N/A	N/A	No	No	N/A	N/A	N/A
The association between blood PFAS concentrations and clinical biochemical measures of organ function and metabolism in participants of the Canadian Health Measures Survey (CHMS) (10.1016/j.scitotenv.2022.153900)	2022	Other	Serum	**Yes**	N/A	No	No	N/A	N/A	**Yes**
A prospective nested case-control study of serum concentrations of per- and polyfluoroalkyl substances and aggressive prostate cancer risk (10.1016/j.envres.2023.115718)	2023	Cancer	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	No
Association among serum per- and polyfluoroalkyl substances, lipid profile and metabolic syndrome in Czech adults, HBM-EHES Survey 2019 (10.21101/cejph.a7799)	2023	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes***

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Association between maternal exposure to per- and polyfluoroalkyl substances and serum markers of liver function during pregnancy in China: A mixture-based approach (10.1016/j.envpol.2023.121348)	2023	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Association between polyfluoroalkyl substances exposure and sex steroids in adolescents: The mediating role of serum albumin (10.1016/j.ecoenv.2023.114687)	2023	Endocrine	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association between prenatal exposure to perfluoroalkyl substance mixtures and intrauterine growth restriction risk: A large, nested case-control study in Guangxi, China (10.1016/j.ecoenv.2023.115209)	2023	Development	Serum	**Yes**	No	No	No	No	No	**Yes**
Association of Early Pregnancy Perfluoroalkyl and Polyfluoroalkyl Substance Exposure With Birth Outcomes (10.1001/jamanetworkopen.2023.14934)	2023	Development	Plasma	No	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association of per- and polyfluoroalkyl substance exposure with fatty liver disease risk in US adults (10.1016/j.jhepr.2023.100694)	2023	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association of Per- and Polyfluoroalkyl Substances with Allostatic Load Stratified by Herpes Simplex Virus 1 and 2 Exposure (10.3390/toxics11090745)	2023	Immune	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association of per- and polyfluoroalkyl substances with hepatic steatosis and metabolic dysfunction-associated fatty liver disease among patients with acute coronary syndrome (10.1016/j.ecoenv.2023.115473)	2023	Other	Plasma	**Yes**	No	No	No	**Yes**	No	**Yes**
Associations between endocrine disruptor contamination and thyroid hormone homeostasis in Belgian type 1 diabetic children (10.1007/s00420-023-01974-9)	2023	Endocrine	Serum	**Yes**	No	No	No	No	No	No
Associations between per- and polyfluoroalkyl substances, liver function, and daily alcohol consumption in a sample of US adults (10.1016/j.envres.2023.116651)	2023	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Associations between the chemical exposome and pregnancy induced hypertension (10.1016/j.envres.2023.116838)	2023	Cardiovascular	Plasma	No	**Yes**	No	No	No	No	**Yes**
Associations of exposure to per- and polyfluoroalkyl substances mixture with the numbers of lymph nodes in colorectal cancer patients (10.1016/j.envres.2023.117529)	2023	Cancer	Serum	No	**Yes**	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Associations of Gestational Perfluoroalkyl Substances Exposure with Early Childhood BMI z-Scores and Risk of Overweight/Obesity: Results from the ECHO Cohorts (10.1289/EHP11545)	2023	Other	Serum	**Yes**	No	No	No	**Yes**	No	No
Associations of perfluoroalkyl substances with adipocytokines in umbilical cord serum: A mixtures	2023	Other	Serum	**Yes**	No	**Yes**	No	No	**Yes**	**Yes**
Associations of Prenatal Per- and Polyfluoroalkyl Substance (PFAS) Exposures with Offspring Adiposity and Body Composition at 16–20 Years of Age: Project Viva (10.1289/EHP12597)	2023	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Birth Outcomes in Relation to Prenatal Exposure to Per- and Polyfluoroalkyl Substances and Stress in the Environmental Influences on Child Health Outcomes	2023	Development	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Cardiometabolic health and per and polyfluoroalkyl substances in an Inuit population (10.1016/j.envint.2023.108283)	2023	Lipid	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Case-Cohort Study of the Association between PFAS and Selected Cancers among Participants in the American Cancer Society's Cancer Prevention Study II LifeLink	2023	Cancer	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes***
Contact to perfluoroalkyl substances and thyroid health effects: A meta-analysis directing on pregnancy (10.1016/j.chemosphere.2023.137748)	2023	Endocrine	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Cross-sectional associations of maternal PFAS exposure on SARS-CoV-2 IgG antibody levels during pregnancy (10.1016/j.envres.2022.115067)	2023	Immune	Plasma	**Yes**	No	No	No	No	**Yes**	**Yes**
Effect of lifestyle-based lipid lowering interventions on the relationship between circulating levels of per-and polyfluoroalkyl substances and serum cholesterol (10.1016/j.etap.2023.104062)	2023	Lipid	Serum	**Yes**	No	No	No	**Yes**	**Yes**	**Yes**
Environmental Exposure to Emerging Alternatives of Per- and Polyfluoroalkyl Substances and Polycystic Ovarian Syndrome in Women Diagnosed with Infertility: A Mixture (10.1289/EHP11814)	2023	Other	Serum	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Exploratory profiles of phenols, parabens, and per- and poly-fluoroalkyl substances among NHANES study participants in association with previous cancer diagnoses (10.1038/s41370-023-00601-6)	2023	Cancer	Serum	No	**Yes**	N/A	No	No	No	**Yes**
Exposure to per- and polyfluoroalkyl substances and glycemic control in older US adults with type 2 diabetes mellitus (10.1016/j.envres.2022.114697)	2023	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Exposure to per- and polyfluoroalkyl substances in early pregnancy, risk of gestational diabetes mellitus, potential pathways, and influencing factors in pregnant women: A nested case-control study (10.1016/j.envpol.2023.121504)	2023	Other	Serum	No	**Yes**	No	No	No	**Yes**	**Yes**
Gestational hypertension, preeclampsia, and gestational dia	2023	ipids; Endocrin	ing water; s	**Yes**	No	No	No	**Yes**	**Yes**	No
Human serum poly- and perfluoroalkyl substance concentrations and their associations with gestational diabetes mellitus (10.1016/j.envpol.2022.120833)	2023	Endocrine	Serum	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Immune response to COVID-19 vaccination in a population with a history of elevated exposure to per- and polyfluoroalkyl substances (PFAS) through drinking water (10.1038/s41370-023-00564-8)	2023	Immune	Drinking water; serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	No
Liver and cardiometabolic markers and conditions in a cross-sectional study of three Australian communities living with environmental per- and polyfluoroalkyl substances contamination (10.1016/j.envres.2023.115621)	2023	Lipids, Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Maternal Serum Concentrations of Per- and Polyfluoroalkyl Substances in Early Pregnancy and Small for Gestational Age in Southern Sweden (10.3390/toxics11090750)	2023	Development	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Mediating effect of endocrine hormones on association between per- and polyfluoroalkyl substances exposure and birth size: Findings from sheyang mini birth cohort study (10.1016/j.envres.2023.115658)	2023	Development; Endocrine	Serum	No	**Yes**	No	No	No	No	**Yes**
Per- and Polyfluoroalkyl Substances (PFAS) and Lipid Trajectories in Women 45-56 Years of Age: The Study of Women's Health Across the Nation (10.1289/EHP12351)	2023	Lipid	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Per- and Polyfluoroalkyl Substances (PFAS) in Community Water Systems (CWS) and the Risk of Thyroid Cancer: An Ecological Study (10.3390/toxics11090786)	2023	Cancer	Drinking water	No	**Yes**	No	No	No	**Yes**	**Yes**
Per- and Poly-fluoroalkyl Substances and Bile Acid Profiles in Pregnant Women (10.1021/acs.est.3c05106)	2023	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Per- and polyfluoroalkyl substances, gestational weight gain, postpartum weight retention and body composition in the UPSIDE cohort (10.1186/s12940-023-01009-3)	2023	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Perfluoroalkyl Acids in Follicular Fluid and Embryo Quality during IVF A Prospective IVF Cohort in China (10.1289/EHP10857)	2023	Development	Follicular fluid	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Perfluoroalkyl substance (PFAS) exposure and risk of nonalcoholic fatty liver disease in the elderly: results from NHANES 2003-2014 (10.1007/s11356-023-26941-2)	2023	Other	Serum	No	**Yes**	No	No	No	**Yes**	**Yes**
Perfluoroalkyl substances (PFAS) and lead (Pb) as cardiovascular disruptors in 9-11-year-old children living in Syracuse, New York, United States (10.1016/j.envres.2023.116758)	2023	Cardiovascular	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Positive Associations of Perfluoroalkyl and Polyfluoroalkyl Substances With Hypertension May Be Attenuated by Endogenous Sex Hormones: A Nationally Representative Cross-Sectional Study (10.1161/hypertensionaha.123.22127)	2023	Development	Serum	No	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Prenatal and childhood exposure to per-/polyfluoroalkyl sub	2023	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Prenatal exposure to legacy PFAS and neurodevelopment in preschool-aged Canadian children: The MIREC cohort (10.1016/j.ntt.2023.107181)	2023	Other	Serum	**Yes**	No	No	No	**Yes**	**Yes**	No
Prenatal Exposure to Multiple Endocrine-Disrupting Chemicals and Childhood BMI Trajectories in the INMA Cohort Study (10.1289/EHP11103)	2023	Development	Plasma	No	**Yes**	No	No	No	No	**Yes**
Prenatal exposure to per- and polyfluoroalkyl substances and pregnancy outcome in Austria (10.1016/j.ecoenv.2023.115006)	2023	Development	Serum	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Prenatal exposure to perfluoroalkyl substances and inflammatory biomarker concentrations (10.1097/EE9.0000000000000262)	2023	Other	Serum	**Yes**	No	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Prenatal per- and polyfluoroalkyl substances (PFAS) exposure in relation to preterm birth subtypes and size-for-gestational age in the LIFECODES cohort 2006-2008 (10.1016/j.envres.2023.116967)	2023	Development	Plasma	No	**Yes**	No	No	No	No	**Yes**
Prenatal perfluoroalkyl substances exposure and maternal sex steroid hormones across pregnancy (10.1016/j.envres.2023.115233)	2023	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma in the Multiethnic Cohort Study (10.1016/j.envint.2023.108197)	2023	Cancer	Serum	No	**Yes**	No	No	No	No	**Yes**
Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population (10.1016/j.envint.2018.05.051)	2023	Cardiovascular	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
The association between endocrine disrupting chemicals and MAFLD: Evidence from NHANES survey (10.1016/j.ecoenv.2023.114836)	2023	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
The Association of Perfluoroalkyl Substance Exposure and a Serum Liver Function Marker in Korean Adults (10.3390/toxics11120965)	2023	Other	Serum	**Yes**	**Yes**	N/A	No	**Yes**	**Yes**	**Yes**
The role of exposure to per- and polyfluoroalkyl substances in racial/ethnic disparities in hypertension: Results from the study of Women?s health across the nation (10.1016/j.envres.2023.115813)	2023	Cardiovascular	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Unveiling Distribution of Per- and Polyfluoroalkyl Substances in Matched Placenta-Serum Tetrads: Novel Implications for Birth Outcome Mediated by Placental	2023	Development	Serum, placenta	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Adverse birth outcomes related to concentrations of per- and polyfluoroalkyl substances (PFAS) in maternal blood collected from pregnant women in 1960-1966 (10.1016/j.envres.2023.117010)	2024	Development	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association between exposure to per- and perfluoroalkyl sul	2024	Endocrine	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association between exposure to per- and polyfluoroalkyl substance and liver injury in American adults (10.7555/JBR.38.20240018)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Association between mixed exposure to per- and polyfluoroalkyl substances and metabolic syndrome in Korean adults: Data from the Korean National environmental health survey cycle 4 (10.1016/j.ijheh.2024.114427)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association between per- and poly-fluoroalkyl substances and nonalcoholic fatty liver disease: A nested case-control study in northwest China (10.1016/j.envpol.2024.123937)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association between per- and polyfluoroalkyl substances exposure and thyroid function biomarkers among females attending a fertility clinic (10.1016/j.envpol.2024.123513)	2024	Other	Serum	No	**Yes**	No	No	No	No	**Yes**
Association between perfluoroalkyl and polyfluoroalkyl substances exposure and fetal overgrowth: A prospective birth cohort study conducted in China (10.1016/j.envres.2023.116175)	2024	Development	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Association between prenatal exposure to per- and polyfluoroalkyl substances and infant anthropometry: A prospective cohort study (10.1016/j.ijheh.2024.114339)	2024	Other	Serum	No	**Yes**	No	No	No	**Yes**	**Yes**
Association between serum perfluoroalkyl substances concentrations and non-alcoholic fatty liver disease among Korean adults: a cross-sectional study using the National Environmental Health Survey cycle 4 (10.35371/aoem.2024.36.e10)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Association of co-exposure to organophosphate esters and per- and polyfluoroalkyl substances and mixture with cardiovascular-kidney-liver-metabolic biomarkers among Chinese adults (10.1016/j.ecoenv.2024.116524)	2024	Cardiovascular	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Association of exposure to multiple perfluoroalkyl and polyfluoroalkyl substances and glucose metabolism in National Health and Nutrition Examination Survey 2017-2018 (10.3389/fpubh.2024.1370971)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Associations between per- and polyfluoroalkyl chemicals and abdominal aortic calcification in middle-aged and older	2024	Cardiovascular	Serum	**Yes**	**Yes**	No	No	No	No	**Yes**
Associations of per- and polyfluoroalkyl substances and nonalcoholic fatty liver disease in the United States adult population, 2003-2018 (10.1097/EE9.0000000000000284)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Associations of per- and polyfluoroalkyl substances with maternal early second trimester sex-steroid hormones (10.1016/j.ijheh.2024.114380)	2024	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Associations of per- and polyfluoroalkyl substances with maternal metabolic and inflammatory biomarkers in early-to-mid-pregnancy (10.1016/j.envres.2024.118434)	2024	Immune	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Associations of perfluoroalkyl substances with metabolic-associated fatty liver disease and non-alcoholic fatty liver disease: NHANES 2017-2018 (10.1007/s10552-024-01865-5)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Associations of Serum Perfluoroalkyl Substances and Placental Human Chorionic Gonadotropin in Early Pregnancy, Measured in the UPSIDE Study in Rochester, New York (10.1289/EHP12950)	2024	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Asthma and Decreased Lung Function in Children Exposed to Perfluoroalkyl and Polyfluoroalkyl Substances (PFASs): An Updated Meta-Analysis Unveiling Research Gaps (10.1016/j.envres.2024.119827)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Biochemical and haematological effects of serum PFOA, ADV and cC6O4 in workers of a chemical company producing fluoropolymers Italy, 2013-2022 (10.1016/j.ijheh.2024.114440)	2024	Lipids	Serum	No	No	No	No	No	**Yes**	No
Distribution of per- and polyfluoroalkyl substances in blood, serum, and urine of patients with liver cancer and associations with liver function biomarkers (10.1016/j.jes.2023.05.026)	2024	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Early menarche and other endocrine disrupting effects of per- and polyfluoroalkyl substances (PFAS) in adolescents from Northern Norway. The Fit Futures study (10.1016/j.envres.2023.117703)	2024	Endocrine	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Early-life exposure to perfluoroalkyl substances and serum antibody concentrations towards common childhood vaccines in 18-month-old children in the Odense Child	2024	Immune	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	Key PFAS cause signifcant effect?
Epidemic-specific association of maternal exposure to per- and polyfluoroalkyl substances (PFAS) and their components with maternal glucose metabolism: A cross-sectional analysis in a birth cohort from Hong Kong (10.1016/j.scitotenv.2024.170220)	2024	Other	Serum	No	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Exploring the impact of prenatal perfluoroalkyl and polyfluoroalkyl substances exposure on blood pressure in early childhood: A longitudinal analysis (10.1016/j.ecoenv.2024.116220)	2024	Cardiovascular	Plasma	**Yes**	No	No	No	No	No	**Yes**
Exposure to per- and polyfluoroalkyl substance and metabolic syndrome: A nationally representative cross-sectional study from NHANES, 2003-2018 (10.1016/j.envpol.2024.123615)	2024	Other	Serum	**Yes**	**Yes**	No	No	No	No	**Yes**
Exposure to per- and polyfluoroalkyl substances and breast cancer risk: a systematic review and meta-analysis of epidemiologic studies (10.1093/aje/kwae010)	2024	Cancer	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Exposure to per- and polyfluoroalkyl substances, neonicotinoid insecticides, benzotriazoles and benzothiazoles: Associations with human non-alcoholic fatty liver disease (10.1016/j.enceco.2024.07.005)	2024	Other	Serum	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Exposure to Perfluoroalkyl Substances and Hyperlipidemia Among Adults Data From NHANES 2017-2018 (10.1097/JOM.0000000000003000)	2024	Lipids	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Exposure to perfluoroalkyl substances and longitudinal changes in bone mineral density in adolescents and young adults: A multi-cohort study (10.1016/j.envres.2023.117611)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Individual and joint associations of per- and polyfluoroalkyl substances (PFAS) with gallstone disease in adults: A cross-sectional study (10.1016/j.chemosphere.2024.142168)	2024	Other	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	No
Influence of maternal endocrine disrupting chemicals exposure on adverse pregnancy outcomes: A systematic review and meta-analysis (10.1016/j.ecoenv.2023.115851)	2024	Development	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**

Title (DOI)	Year	Outcome Category	Exposure Route Assessed	Key epidemiological study for						Key PFAS cause signifcant effect?
				PFHxS	PFNA	PFBS	HFPO-DA	PFOS	PFOA	
Maternal and Paternal Preconception Serum Concentrations of Per and Polyfluoroalkyl Substances in Relation to Birth Outcomes (10.1021/acs.est.3c07954.)	2024	Development	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**
Maternal serum concentrations of per- and polyfluoroalkyl substances and childhood acute lymphoblastic leukemia (10.1093/jnci/djad261)	2024	Cancer	Serum	No	No	No	No	**Yes**	No	**Yes**
Per- and polyfluoroalkyl substances (PFAS) and fetal growth: A nation-wide register-based study on PFAS in drinking water (10.1016/j.envint.2024.108727)	2024	Development	Drinking Water	No	**Yes**	No	No	**Yes**	No	**Yes**
Per- and polyfluoroalkyl substances and bone mineral content in early adolescence: Modification by diet and physical activity (10.1016/j.envres.2024.118872)	2024	Other	Serum	No	No	No	No	**Yes**	No	No
PFAS alters placental arterial vasculature in term human placentae: A prospective pregnancy cohort study (10.1016/j.placenta.2024.03.002)	2024	Other	Serum	**Yes**	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**
Prenatal exposure to poly/perfluoroalkyl substances and risk for congenital heart disease in offspring (10.1016/j.jhazmat.2024.134008)	2024	Cardiovascular	Plasma	No	**Yes**	No	No	No	No	**Yes**
Thyroid cancer and endocrine disruptive chemicals: a case-control study on per-fluoroalkyl substances and other persistent organic pollutants (10.1530/ETJ-23-0192)	2024	Cancer	Serum	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**