Perfluorooctanoic acid (PFOA) | 2019

Substance Overview

Perfluorooctanoic acid (PFOA) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS). Because of its chemical properties, PFOA has been used as stain repellants in commercial products like carpet and fabric, as a coating for packaging, and in some fire-fighting foams.[1] PFOA can persist in the environment and in the body for long periods of time.[1]

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for PFOA.

DHS recommends a combined enforcement standard of 20 nanograms per liter (ng/L) for PFOA. The recommended standard is based on a study that used modeling to estimate how much PFOA a mother has to be exposed to in order to protect the infant from developmental effects. **This standard applies to the sum of PFOA and PFOS concentrations in groundwater.**

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for PFOA be set at 10% of the enforcement standard because PFOA has been shown to have carcinogenic, teratogenic, and interactive effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

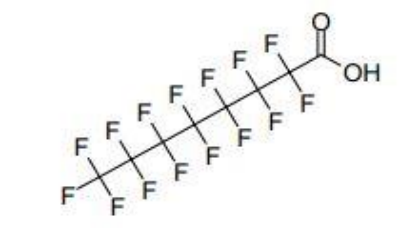
Recommended Standards	
Enforcement Standard:	20 ng/L
Preventive Action Limit:	2 ng/L
(Sum of PFOA and PFOS)	

Health Effects

Studies in workers and people living in areas with high levels of PFOA show that PFOA may increase cholesterol, damage the liver, cause pregnancy-induced hypertension, increase the risk for thyroid disease, decrease antibody response to vaccines, decrease fertility, and cause small decreases in birth weight.[1] Studies in research animals have found that PFOA can cause damage to the liver and the immune system, birth defects, delayed development, and newborn deaths in lab animals.[1]

The International Agency for Research on Cancer (IARC) classifies PFOA as possibly carcinogenic to humans and the EPA states there is suggestive evidence of carcinogenic potential for PFOA. PFOA has been shown to be genotoxic in some tests, but has not been shown to be mutagenic.[2,3] Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOA can cause interactive effects.[1,4,5]

Chemical Profile

	PFOA
Structure:	
CAS Number:	335-67-1
Formula:	C8HF15O2
Molar Mass:	414.069 g/mol
Synonyms:	Perfluorooctanoic acid Pentadecafluoro-1-octanoic acid pentadecafluoro-n-octanoic acid pentadecafluoroctanoic acid perfluorocaprylic acid perfluoroheptanecarboxylic acid 2,2,3,3,4,4,5,5,6,6,7,7,8,8, 8-pentadecafluoro octanoic acid

Exposure Routes

People can be exposed to PFOA by drinking contaminated water, eating fish caught from contaminated waterbodies, swallowing contaminated soil or dust, eating food that was packaged in material that contains PFOA, and using consumer products such as non-stick cookware, stain resistant carpeting, and water repellant clothing.[1]

Research has shown that the majority of exposure to PFOA comes from food. Drinking water can be a major source of PFOA if levels are high.[1] Babies born to mothers exposed to PFOA can be exposed during pregnancy and during breastfeeding.[1]

Current Standard

There are no current groundwater standards for PFOA in Wisconsin.[6]

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Lifetime Health Advisory Level:	70 ng/L	(2016)
Drinking Water Concentration (Cancer Risk):	500 ng/L	(2016)

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose:	0.00002 mg/kg-d (20 ng/kg-d)	(2016)

Oncogenic Potential

EPA Cancer Slope Factor:	0.07 $(mg/kg\text{-}d)^{-1}$	(2016)

Guidance Values

ATSDR Minimum Risk Level:	0.000003 mg/kg-d (3 ng/kg-d)	(2018)

Literature Search

Search Dates:	2016 – 2019
Total studies evaluated:	Approximately 280
Key studies found:	Yes

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for PFOA.[7]

Health Advisory Level

In 2016, the EPA published a lifetime Health Advisory of 70 ng/L for PFOA.[2,3] The EPA evaluated several studies including those that observed effects on immune response, development, and liver and kidney toxicity. They selected a 2006 study by Lau et al. as the critical study.[8] In this study, the researchers gave pregnant mice different concentrations of PFOA (0, 1, 3, 5, 10, 20, or 40 mg/kg-d) by gavage during pregnancy (GD 1 to 17). In these mice, PFOA caused early pregnancy loss, compromised postnatal survival, delayed general growth and development, and sex-specific alterations in pubertal maturation. The EPA identified a Lowest Observable Adverse Effect Level (LOAEL) of 1 milligram PFOA per kilogram body weight per day

Summary of EPA's Health Advisory for PFOA	
LOAEL:	1 mg/kg-d (1,000,000 ng/kg-d)
Half-life used:	2.3 years
Human equivalent dose:	0.0053 mg/kg-d (530 ng/kg-d)
Total uncertainty factor:	300
Oral reference dose:	0.00002 mg/kg-d (20 ng/kg-d)
Water Concentration:	**70 ng/L**

(mg/kg-d) based on decreased bone development and accelerated male puberty in offspring after maternal exposure from this study.

Pharmacokinetic models are mathematical modeling techniques that can be used to predict the movement of chemicals in the body. The EPA used pharmacokinetic modeling for PFOA to estimate a human equivalent dose, which is the amount that a person would have to ingest every day to cause this effect. The model used by EPA converted the level of PFOA in animal serum at which adverse effects were observed to a corresponding level in human serum. The human equivalent dose was then estimated by taking into consideration the amount of time that PFOA stays in the body (half-life) and how much blood is in the human body.

The EPA estimated a human equivalent dose of 530 ng/kg-d for PFOA by using the LOAEL and a half-life of 2.3 years. The EPA selected the half-life a 2010 study by Bartell et al.[9] This study estimated half-life after treatment was installed to remove PFOA from the water supply in Lubeck, WV and Little Hocking, OH. The EPA's rationale for selecting this study is that it applies to the general population and reflects exposure that is primarily from drinking water.

The EPA applied a total uncertainty factor of 300 to account for differences between people and research animals (3), differences among people (10), and the use of a LOAEL instead of a NOAEL (10). This resulted in an oral reference dose of 20 ng/kg-d. To set the advisory, the EPA used a water consumption rate for pregnant women (0.054 liters per kilogram body weight per day or L/kg-d) because the effect occurred in offspring after the maternal exposure during pregnancy. They applied the default relative source contribution of 20% to account for exposure from other sources (such as food and air).

The EPA recommended that the lifetime health advisory of 70 ng/L apply to the sum of PFOA and PFOS. They recommended this combined approach because the adverse effects in humans and animals are the same or similar and the critical effect used to set the oral reference dose for both PFOA and PFOS are developmental endpoints.

Drinking Water Concentration as Specified Risk Levels

In 2016, EPA also determined a drinking water concentration that corresponds to a lifetime cancer risk of 1 in 1,000,000 for PFOA.[2] They used a cancer slope factor of 0.07 $(mg/kg\text{-}d)^{-1}$ (see *EPA Cancer Slope Factor* section below for more details), an average body weight of 80 kg, and a daily water consumption rate of 2.5 L/d to calculate a water concentration of 500 ng/L. Because this concentration is higher than the level that was calculated to protect against developmental effects, the EPA concluded that the lifetime health advisory of 70 ng/L is protective of potential cancer effects.

State Drinking Water Standard

Chapter 160, Wis. Stats., 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 PFOA.[6]

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, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

In setting the lifetime health advisory for PFOA, the EPA Office of Water established an oral reference dose of 20 ng/kg-d (see above for more details).[2,3]

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS 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 PFOA, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of PFOA. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

In 2016, the EPA also evaluated the cancer potential of PFOA when developing the health advisory and determined that there is suggestive evidence that PFOA has carcinogenic potential in humans.[2,3]

The International Agency for Research on Cancer (IARC) have not evaluated the cancer potential of PFOA.[10]

EPA Cancer Slope Factor

In 2016, the EPA established a cancer slope factor of 0.07 $(mg/kg\text{-}d)^{-1}$ from a 2012 study by Butenhoff that that evaluated effects in rats exposed to PFOA by gavage for 2 years.[2,3,11] The slope factor is based off an increased incidence of testicular cancer in male rats.

Additional Technical Information

Chapter 160, Wis. Stats., 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 values that have been published since 2016 when the EPA published their health advisory level. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Risk Level (draft)

In 2018, the Agency for Toxic Substances and Disease Registry (ATSDR) released a draft Toxicological Profile for Perfluoroalkyls.[1] In this Profile, they recommended an intermediate oral minimum risk level of 3 ng/kg-d for PFOA.[a]

Summary of ATSDR's Minimum Risk Level for PFOA	
LOAEL:	0.3 mg/kg-d (300,000 ng/kg-d)
Half-life used:	3.8 years
Human equivalent dose:	0.000821 mg/kg-d (821 ng/kg-d)
Total uncertainty factor:	300
Minimum risk level:	0.000003 mg/kg-d (3 ng/kg-d)

The ATSDR evaluated several studies including those that observed effects on immune response, development, and liver toxicity. They selected two studies as their critical studies: a 2011 study by Onishchenko et al.[12] and a 2016 study by Koskela et al.[13] In these studies, 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 from these studies.

The ATSDR also used pharmacokinetic modeling to estimate a human equivalent dose by converting the level of PFOA in animal serum to a level in serum that would cause the same effect in humans. They estimated a human equivalent dose of 821 ng/kg-d for PFOA by using the LOAEL and a half-life of 3.8 years. The ATSDR selected this half-life from a 2007 study by Olsen et al that estimated the half-life in occupationally-exposed workers.[14] The ATSDR selected this study because the follow-up time was longer than the Bartell et al., 2010 study (more than 5 years in the Olsen et al. study compared to 6-12 months in the Bartell et al. study) and that a study found that estimates of the terminal half-life for PFOA can increase with longer follow-up.[15]

To obtain the intermediate oral minimum risk level, the 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).

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a The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not recommend a chronic oral reference dose for PFOA because they felt that that the available data for chronic exposure (more than 1 year) are limited and were uncertain whether the most sensitive endpoint for chronic exposure has been identified in the current research.

Literature Search

The ATSDR's draft Toxicological Profile on PFAS was published in June 2018. The last literature search conducted by the ATSDR was done in May 2016. To identify recent publications, we conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2016 to April 2019. We searched for studies related to PFOA toxicity or PFOA effects on a disease state in which information on exposure or dose was included as part of the study or studies related to modeling PFOA exposure or dose using pharmacokinetics in animals or humans.[b] Previous research has shown that effects on the immune system, development, and reproduction are the most sensitive, so we searched for new toxicity studies in these areas.[1,2] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an appropriate exposure duration.

Approximately 280 studies were returned by the search engine. We excluded studies on non-mammalian or cell systems, non-oral exposure routes, those that did not evaluate health risks, and those only examining a single point of exposure from further review. After applying these exclusion criteria, we located five key toxicity studies and three key pharmacokinetic studies on PFOA.

To be considered a critical toxicity study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.[c] Four of the key studies met the criteria to be considered a critical toxicity study (see Tables A-1 and A-2 for more details). To be considered a critical pharmacokinetics study, the study must model oral exposure in humans or rodents. Three of the key studies met the criteria to be considered a critical pharmacokinetic study (the section below has more details on these studies).

Critical Toxicity Studies

To compare between results between studies, we calculated acceptable daily intake (ADI) for each study/effect. The ADI is the estimated amount of PFOA that a person can be exposed to every day and not experience health impacts. The ADI equals the toxicity value divided by the total uncertainty factor. Uncertainty factors were included as appropriate to account for differences between humans and research animals, differences in sensitivity to health effects within human populations, using data from short-term experiments to protect against effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

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b The following search terms were used in the literature review:
Title/abstract: PFOA or "Perfluorooctane sulfonate"
Keywords: Development OR immune OR reproduction OR pharmacokinetics OR modeling
Subject area: toxicology OR cancer
Language: English

c Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).[8]

Chen et al., 2017

In 2017, Chen et al. evaluated the effects of PFOA exposure by gavage on development.[16] Pregnant mice were exposed to 2.5, 5, or 10 mg/kg-d of PFOA from gestational days (GD) 1 to 7 or 1 to 13. The highest concentration of PFOA significantly increased the number of resorbed embryos at GD13. All doses of PFOA affected serum progesterone levels and decreased transcription levels of key steroidogenic enzymes.

From this study, we identified a LOAEL of 2.5 mg/kg-d based on altered serum progesterone levels. We estimated an ADI of 0.0025 mg/kg-d based on the LOAEL and a total uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and using a LOAEL instead of a NOAEL (10).

Goulding et al., 2017

In 2017, Goulding et al. evaluated the effects of PFOA exposure by gavage on development.[17] Pregnant mice were exposed to 0.1, 0.3, or 1 mg/kg-d of PFOA from gestational days 1 to 17. In this study, PFOA caused minimal effects on neurological development in male offspring. The only statistically significant effect was higher ambulatory activity in offspring at postnatal day (PND) 18 in mice exposed to 1 mg/kg-d. This effect was not observed at PND 19 and 20. The NOAEL from this study is 0.3 mg/kg-d and the LOAEL is 1 mg/kg-d.

From this study, we identified a NOAEL of 0.3 mg/kg-d and LOAEL of 1 mg/kg-d based on higher ambulatory activity in offspring at PND 18. We estimated an ADI of 0.003 mg/kg-d based on the NOAEL and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Song et al., 2018

In 2018, Song et al. evaluated the effects of PFOA exposure by gavage on development.[18] Pregnant mice were exposed to 1, 2.5, or 5 mg/kg-d of PFOA from gestational days 1 to 17. The highest concentration of PFOA caused a significant decrease in offspring survival. PFOA exposure also caused non-dose respondent serum testosterone level changes and testis structural changes. The NOAEL from this study is 2.5 mg/kg-d and the LOAEL is 5 mg/kg-d.

From this study, we identified a NOAEL of 2.5 mg/kg-d and a LOAEL of 5 mg/kg-d based on decreased offspring survival. We estimated an ADI of 0.025 mg/kg-d based on the NOAEL and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Van Esterik et al., 2016

In 2016, van Esterik et al. evaluated the impact of PFOA exposure *in utero* and during lactation on metabolic effects.[19] Pregnant mice were exposed to 0.003, 0.01, 0.03, 0.1, 0.3, 1, or 3 mg/kg-d of PFOA from gestation through lactation. In this study, PFOA decreased body weight at week 21 and decreased cortical density in the tibia in male offspring. In female offspring, PFOA decreased body weight at week 21 and 27, decreased femur length and weight, decreased quadriceps femoris muscle and perirenal fat

pad weight, and decreased tibia composition/function (including cortical density, ability to resist torsion, bending strength, and trabecular area). PFOA also decreased serum cholesterol and triglycerides levels. The most sensitive effect measured was the effect on serum triglyceride levels in female mice.

From this study, we identified a benchmark dose (95% Lower Confidence Limit) of 0.0062 mg/kg-d PFOA. Based on altered serum triglyceride levels in female mice. We estimated an ADI of 0.000062 mg/kg-d based on the BMDL and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Critical Pharmacokinetic Studies

Cheng and Ng, 2017

In 2017, Cheng and Ng published a study in which they adapted an existing pharmacokinetic model to estimate serum levels of PFOA in rats.[20] The advantage of this model is that it considers cell membrane permeability instead of blood flow rate as the rate limiting process. This is important because large molecules like PFOA are more likely to be limited by cell membrane permeability than blood flow kinetics. This model was used to estimated serum levels of PFOA after exposure to 0.1 and 1 mg/kg-orally and 0.041 and 1 mg/kg intravenously. The authors found that the model was able to predict plasma toxicokinetics and tissue distribution of PFOA within a factor of 5.

Some of the limitations of this model are that some parameter values used are based on a single study or extrapolated from *in vitro* studies, which adds uncertainty to the model predictions. Additionally, some protein-binding parameters were not included and the model did not consider females due to limited data.

Goeden et al., 2019

In 2019, Goeden et al**.** published a study in which they developed a pharmacokinetic model to estimate PFOA serum levels in infants at birth from placental transfer and predict serum levels after early life exposure from bottle- or breastfeeding.[21] In this model, they used a maternal serum concentration of 38 mg/L to estimate PFOA serum levels in infants after bottle and breastfeeding. This maternal serum level corresponds to the dose that caused developmental effects in the Lau et al. study, which was used by EPA to set the LHA. Goeden et al. then used this estimated infant serum level to determine a health-based guidance value for PFOA in drinking water (for more details on this value, see Table A-1).

The authors found that predicted serum concentration following 6 months of breastfeeding aligned closely with reported mean and 95th percentile infant serum concentrations at 6 months of age (R^2 = 0.7044). They also found that predicted infant serum concentrations were 40% higher than previously estimated adult levels when placental transfer was considered and, when both placental transfer and breastmilk transfer are taken into account, infant concentrations are 600% higher than adult steady-state levels.

One limitation of this model is that it assumes the mother's serum concentration at delivery is at steady-state. It also assumes that maternal exposure to PFOA during lactation is the same as prior to delivery and estimates maternal exposure from serum concentration at delivery.

Kieskamp et al., 2018

This study combined two existing models of developmental exposure (one in mice and one in humans) to estimate fetal and pup plasma levels resulting from maternal exposure to the LOAEL used by EPA. They then used these fetal and pup plasma levels to predict the human equivalent dose (HED) in women that would result in fetal and child plasma levels that match the levels in animals. Finally, they evaluated how the estimated HEDs were influenced by breastfeeding duration and half-life by using breastfeeding durations of 6, 12, and 24 months and half-lives of 2.3 and 3.8 years.

The authors obtained a distribution of HEDs for 24 combinations based on estimated dose, half-life, and breastfeeding duration and reported the 1st and 50th percentile estimated HEDs. They found that using the shorter half-life resulted in lower estimated HEDs. They also found that estimated HED generally decreased with increasing breastfeeding duration. All of the predicted HEDs based on pup/child dosimetry were below the adult HED used by EPA to set the health advisory level for PFOA (530 ng/kg-d).

Predicted Human Equivalent Doses (HEDs) for Given Half-Life and Breastfeeding Duration (ng/kg-d)

		1st Percentile		50th Percentile	
	Half-life:	2.3 year	3.8 year	2.3 year	3.8 year
Breastfeeding duration	6 months	99	62	50	43
	12 months	78	50	54	33
	24 months	73	47	70	31
Adapted from Table 1 in Kieskamp et al. 2018 ([22])					

One limitation of this model is that, for some parameters, values from rats were used due to limited available information for mice. The authors noted that additional data in animals and humans would provide better understanding of how PFOA partitions into milk over time and improve estimates of lactational transfer.

Summary

While a large number of epidemiology studies on the effects of PFOA have been published since 2016 (see Appendix B for a summary of these studies), the long half-life of PFOA in people, multiple potential exposure sources, and the ability for other PFAS compounds to cause similar health effects prohibit using these data to establish a health-based value for PFOA.[21,23-117] As such, animal and modeling studies are crucial for the development of a protective standard.

Animal studies published since 2016 indicate that development is a significant endpoint for PFOA and that effects may occur at levels lower than those previously studied.[17-19,101] New modeling studies have better characterized how PFOA levels in infants are affected due to exposure *in utero* and from breastfeeding.[20-22]

Standard Selection

DHS recommends a combined enforcement standard of 20 ng/L for PFOA and PFOS.

There is a federal number for PFOA – EPA's lifetime health advisory level.[2,3] However, recent modeling studies have indicated that the approach used by EPA to set their advisory may not be adequately protective of infants.[21,22]

Basis for Recommended Standard

- ☐ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☑ **Significant technical information**

Toxicity studies in animals continue to show that development is a critical effect for PFOA with effects occurring in offspring after exposure during pregnancy and lactation.[16-19] Recent modeling studies with PFOA have indicated that modeling approach taken by EPA may not be adequate to protect infants from exposure during pregnancy and while breastfeeding.[21,22] PFOA can cross the placenta during pregnancy and pass through breastmilk.[1,2] To set their lifetime health advisory level, the EPA estimated how much PFOA a woman has to be exposed to orally during pregnancy for her serum levels to be equivalent to the level where health effects were seen in mice pups (babies).[2,3] The modeling studies with PFOA modeling of maternal exposure levels may not be adequate to protect infants from exposure during pregnancy and while breastfeeding. These studies suggest that modeling of infant exposure may be a more appropriate approach to protecting this sensitive population.

From this information, DHS concludes that there is significant technical information that was not considered when EPA set the lifetime health advisory for PFOA. Therefore, DHS recommends setting the enforcement standard for PFOA using procedures in s. 160.13(2). DHS selected the 2018 study by Kieskamp et al. as the principal study.[22] In this study, the authors use a model to estimate how much a pregnant woman would have to be exposed to orally for the baby to plasma levels equivalent to the LOAEL used by EPA. They looked at how half-life and breastfeeding duration affected exposure levels.

From this study, we selected the HED of 0.00054 mg/kg-d as the toxicity value, which is the median HED for a half-life of 2.3 years and breastfeeding duration of 12 months. We used the median HED because it represents a more realistic exposure scenario than the 1st percentile HED. We selected the HED that corresponds with the half-life of 2.3 years from the Bartell et al. study.[9] The half-life of 2.3 years is consistent with the half-life reported in a recent study by Li et al.[118] In this 2018 study, researchers estimated half-life after clean water was provided to individuals exposed to municipal drinking water contaminated with a number of PFAS in Ronneby, Sweden. The researchers measured PFOA, PFOS, and PFHxS levels in 104 individuals from June 2014 through September 2016. They estimated a half-life of 2.7 years for PFOA. We selected the HED that corresponds with a breastfeeding duration of 12 months as the American Academy of Pediatrics (AAP) recommends that infants are breastfed for up to 12 months.[119] As such, using a breastfeeding duration of less than 12 months may not provide adequate protection while using a duration of more than 12 months may overestimate PFOA exposure.

We 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). To determine the recommended enforcement standard, DHS used the ADI, and, as required by Ch. 160, Wis. Stats., a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

DHS recommends a combined enforcement standard of 20 ng/L for PFOA and PFOS. Studies have shown that PFOA and PFOS can cause similar effects in humans and in animals. The critical studies used by DHS to establish the ADI for PFOA and PFOS are developmental studies and recent studies have shown that PFOA and PFOS may cause toxicity through similar mechanisms of action. This approach is consistent with that taken by the EPA when developing the lifetime health advisory.[2,3] EPA recommended that the advisory apply to the sum of PFOA and PFOS because the adverse effects in humans and animals are same or similar and the critical effect used to set the oral reference dose for both PFOA and PFOS are developmental endpoints.

DHS recommends a combined preventive action level of 2 ng/L for PFOA and PFOS.

DHS recommends that the preventive action level be set at 10% of the enforcement standard because PFOS and PFOA have both been shown to have carcinogenic and teratogenic effects.[1-3] Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOS can cause interactive effects.[1-3]

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Appendix A: Key Toxicity Studies for PFOA

Table A-1. Toxicity Studies Published since ATSDR's Toxicological Profile

Study Type	Species	Exposure Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Development	Mouse	GD 1-7 GD 1 -13	2.5, 5, 10	Gavage	At GD13, PFOA treatment significantly increased numbers of resorbed embryos at 10 mg/kg. Reduced serum progesterone levels and decreased transcription levels of key steroidogenic enzymes. Reduced number and size of corpora lutea in the ovaries.	LOAEL: 2.5	Chen et al, 2017 ([16])
Development	Mouse	GD 1-17	0.1, 0.3, 1.0	Gavage	Shift in the developmental pattern with an elevated activity level observed at 1.0 mg/kg-d at PND 18-20.	NOAEL: 0.3 LOAEL: 1.0	Goulding et al., 2017 ([17])
Reproduction	Mouse	28 d	1.25, 5, 20	Gavage	Decrease in mated and pregnant females per male mouse and litter size. Blood-testes barrier damage.	NOAEL: 1.25 LOAEL: 5	Lu et al, 2016 ([120])
Development	Mouse	GD 1 -17	1, 2.5, 5	Gavage	Significant decrease in offspring survival at 5 mg/kg Non-dose respondent serum testosterone level changes and testis structural changes	NOAEL: 2.5 LOAEL: 5	Song et al. 2018 ([18])
Development	Mouse	GD 1 – PND 21	0.003, 0.01, 0.03, 0.1, 0.3, 1, 3	Diet	Dose-dependent decrease in body weight from PND 4 to adulthood. Under high fat diet, growth was increased in male offspring and decreased in female offspring in the last 4-6 weeks. Increased liver weights and cellular alterations in offspring. Reduced fat pad weights, serum triglycerides, and cholesterol in female offspring.	BMDL: 0.0062 (triglycerides)	van Esterik et al, 2016 ([19])

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Chen, 2017	✓	✓	✓	**3**	✓	**Yes**
Goulding, 2017	✓	✓	✓	**3**	✓	**Yes**
Lu, 2016	⃠	✓	✓	**3**	✓	No
Song et al. 2018	✓	✓	✓	**3**	✓	**Yes**
Van Esterik, 2016	✓	✓	✓	**7**	✓	**Yes**

To be considered a critical toxicity study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.

Appendix B: Epidemiology Studies of PFAS Published since ATSDR's Toxicological Profile[d]

Category	Examples	Number of Studies
Metabolic	Diabetes (type 1, 2, and gestational), glucose tolerance, insulin resistance, BMI, obesity/overweight, adiposity, cholesterol, triglycerides	41
Birth outcomes	Birth size (weight, length, etc), gestation age, small for gestational age, fetal growth, anogenital distance at birth	25
Neurological	Attention, impulse control, visual and spatial ability, cognitive development, executive function, autism spectrum disorder, intellectual disability	18
Reproductive	Endometriosis, preeclampsia, reproductive hormones, time to pregnancy, fertility, semen characteristics, pregnancy loss, menopause, puberty onset	13
Immune	Asthma, vaccine antibodies, allergic conditions, infectious disease incidence, atopic dermatitis	12
Thyroid	Thyroid hormones, thyroid function	10
Cardiovascular	heart attack, stroke, heart failure, arterial wall stiffness, coronary heart disease, blood pressure, hypertension	7
kidney	Chronic kidney disease, kidney function, glomerular filtration	7
Other	Vitamin D, bone density, lung function, dental carries, gut bacteria and metabolites, mortality,	6
DNA	Telomere length, DNA methylation	5
Liver	ALT (alanine aminotransferase), other liver function biomarkers	4
Cancer	Breast cancer	2

d The following search terms were used in the literature review:
Subject: "(PFOS OR PFOA OR PFAS OR PFC) AND epidemiology
Language: English
We excluded studies that did not evaluate health effects from our analysis.