R-WD-19-29

New Hampshire Department of Environmental Services

Technical Background Report for the June 2019 Proposed Maximum Contaminant Levels (MCLs) and Ambient Groundwater Quality Standards (AGQSs) for Perfluorooctane sulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), and Perfluorohexane sulfonic Acid (PFHxS)

June 28, 2019

STATE OF NEW HAMPSHIRE

Department of Environmental Services

Environmental Health Program

Inter-Department Communication

To: James Martin **Date:** September 3, 2019

From: Jonathan M. Ali, Ph.D. **Cc:** Clark Freise

RE: *Correction to Typo in the June 2019 PFAS MCL Technical Support Document*

It has been brought to the attention of the Permitting & Environmental Health Bureau that there is a typographical error in the description of the perfluorooctane sulfonic acid (PFOS) reference dose (RfD) derivation. Specifically, the last sentence at the bottom of page 10, the current document reads:

> "*As a result, NHDES agreed with the use of the NOAEL (2,620 ng/mL) for IgM suppression (Dong et al., 2011) instead of the lower NOAEL of 674 ng/mL (Dong et al., 2009) as a POD*."

However, on the following page, the point of departure (POD) used for the calculation of the RfD is **2,360 ng/mL** instead of the **2,620 ng/mL** described above. The sentence on page 10 should have referred to the POD as 2,360 ng/mL from Table 1 of Dong et al. (2011), not 2,620 ng/mL. This was an error in the text that was not carried into the calculation of the PFOS RfD (3.0 ng/kg-d), and therefore does not affect the final recommendation of the document for a maximum contaminant level (MCL) of 15 ng/L.

Please contact the NHDES Permitting & Environmental Health Bureau at (603) 271-1370 with any questions regarding this memo, or other issues related to the June 2019 PFAS MCL Technical Support Document.

References

Dong GH, Liu MM, Wang D, et al. 2011. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. Arch Toxicol 85(10):1235-1244.

New Hampshire Department of Environmental Services (NHDES). 2019. Summary Report On the New Hampshire Department of Environmental Services Development of Maximum Contaminant Levels and Ambient Groundwater Quality Standards for Perfluorooctanesulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), And Perfluorohexanesulfonic ACID (PFHxS). https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/r-wd-19-01.pdf

Table of Contents

Abbreviations i
Acknowledgements iii
Section I. Executive Summary 1
Section II. Introduction 2
Section III. Reference Dose Derivation 3
Perfluorooctanoic acid or perfluorooctanoate (PFOA), CAS# 335-67-1 4
Principal study & consideration of health effects 4
Determination of a point of departure 6
Application of uncertainty factors 6
Estimation of a human equivalent oral dose 7
Perfluorooctane sulfonic acid or perfluorooctane sulfonate (PFOS), CAS# 1763-23-1 9
Principal study & consideration of health effects 9
Determination of point of departure 10
Application of uncertainty factors 11
Estimation of a human equivalent oral dose 11
Perfluorononanoic acid or perfluorononanoate (PFNA), CAS# 375-95-1 13
Principal study & consideration of health effects 13
Determination of a point of departure 14
Application of uncertainty factors 14
Estimation of a human equivalent oral dose 15
Perfluorohexane sulfonic acid or perfluorohexane sulfonate (PFHxS), CAS# 355-46-4 17
Principal study & consideration of health effects 17
Determination of a point of departure 18
Application of uncertainty factors 18
Estimation of a human equivalent oral dose 19
Summary of Recommended RfDs for PFOA, PFOS, PFNA and PFHxS 21
Recommended RfDs 21
Discussion of scientific uncertainties 21
Section IV. Drinking Water Exposure Assumptions, Modeling and Resulting MCLs 25
Application of Goeden et al. (2019) for exposure modeling 26
Human half-life and V_d assumptions 26
Placental & breastmilk transfer ratios 28

Duration of breastfeeding 28
Breastmilk and drinking water ingestion rate assumptions 29
Consideration of the Relative Source Contribution (RSC) 30
Section V. Discussion of the MCLs proposed by NHDES 34
Modeled Exposure Results 34
Limitations and uncertainties 36
Conclusions 37
References 38

Abbreviations

AFFF - aqueous film forming foam

AGQS - Ambient Groundwater Quality Standard

APFO – ammonium perfluorooctanoate

ATSDR – Agency for Toxic Substances and Disease Registry

BMD – benchmark dose

BMDL – benchmark dose lower-bound confidence limit

C8 – an alternative name for perfluorooctanoic acid

CAR – constitutive androstane receptor

CAS# - Chemical Abstracts Service Registry Number

CDC – Centers for Disease Control and Prevention

CSF – cancer slope factor

d - day

DAF – dosimetric adjustment factor

IR – ingestion rate

IRIS - Integrated Risk Information System

kg - kilogram

L - liter

LHA – lifetime health advisory

Ln – natural logarithm

LOAEL – lowest observed adverse effect level

MCL – maximum contaminant level

mg - milligram

MDH – Minnesota Department of Health

MRL – minimal risk level

ng - nanogram

NHDES – New Hampshire Department of Environmental Services

NH DHHS – New Hampshire Department of Health & Human Services

NIS - National Immunization Survey

NJDWQI – New Jersey Drinking Water Quality Institute

NOAEL – no observed adverse effect level

NTP – National Toxicology Program

PFAS – perfluoroalkyl substances

PFHxS – perfluorohexane sulfonic acid

PFNA – perfluorononanoic acid

PFOA – perfluorooctanoic acid

PFOS – perfluorooctane sulfonic acid

POD – point of departure

PPAR - peroxisome proliferator-activated receptor

ppb –parts-per-billion

ppt – parts-per-trillion

RME – reasonable maximum exposure

RSC – relative source contribution

$t_{1/2}$ – half-life

UF – uncertainty factor

USEPA – U.S. Environmental Protection Agency

V_d – volume of distribution

WHO – World Health Organization

α – alpha, used to denote specific subtypes of biological molecules (i.e., proteins)

β – beta, used to denote specific subtypes of biological molecules (i.e., proteins)

γ - gamma, used to denote specific subtypes of biological molecules (i.e., proteins)

Acknowledgements

New Hampshire Department of Environmental Services would like to thank the numerous New Hampshire stakeholders and residents who provided valuable technical commentary on the initially proposed MCLs for PFOA, PFOS, PFNA and PFHxS. This includes New Hampshire's residents, academic institutions, community advocacy groups, representatives for the business community and municipalities. The science followed in deriving the currently proposed maximum contaminant levels was enacted in part as a result of their contributions. Additionally, NHDES is grateful for insights and information shared by professionals from other state agencies, interstate collaborative working groups and professional societies.

Section I. Executive Summary

The objective of the health-based risk assessment was identifying drinking water concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) that provide adequate protection of human health at all life stages, including but not limited to pre-natal development. This document provides the technical basis for the proposed maximum contaminant levels (MCLs,) which by law become Ambient Groundwater Quality Standards (AGQSs), following evaluation of technical comments submitted up to April 12th, 2019, public comment deadline, as well as peer-reviewed scientific literature published since January 1st, 2019, and external review by Dr. Stephen Roberts at the University of Florida. As a result of this process, NHDES is proposing the following maximum contaminant levels (MCLs):

- **12 ng/L for Perfluorooctanoic acid, or perfluorooctanoate (PFOA)**
- **15 ng/L for Perfluorooctane sulfonic acid, or perfluorooctane sulfonate (PFOS)**
- **11 ng/L for Perfluorononanoic acid, or perfluorononanoate (PFNA)**
- **18 ng/L for Perfluorohexane sulfonic acid, or perfluorohexane sulfonate (PFHxS)**

These health-based values are intended as health-protective limits against the chronic health effects for a through-life exposure. The primary associated health outcomes are hepatotoxicity and changes in lipid metabolism (PFOA and PFNA), suppressed immune response to vaccines (PFOS) and impaired female fertility (PFHxS). Secondary associated health effects that are expected to be less sensitive are changes in thyroid and sex hormone levels, early-life growth delays, changes in cholesterol levels and biomarkers of liver function, neurobehavioral effects, and a possible risk for certain cancers (i.e., testicular and kidney cancer).

These proposed MCLs are lower than those proposed in January 2019 (NHDES 2019) as a result of new studies and models that indicate the standards need to be lower to be adequately protective of health at all life stages. Specifically, a peer reviewed toxicokinetic model was published by the Minnesota Department of Health (Goeden et al., 2019) that predicts blood serum levels across a lifetime. Using similar studies as those from the initial proposal and those suggested in technical comments submitted by April 12th, 2019, this model indicates lower standards are necessary to avoid unacceptable elevations in the serum levels of breastfed infants and children who were breastfed as infants.

The technical basis for the proposed MCLs is detailed in Sections III and IV, and the modeling results and conclusions are presented in Section V. Briefly, this risk assessment utilized upper value, “conservative” estimates regarding: daily water consumption rates throughout life, breastmilk consumption rates through infancy, the duration of exclusive breastfeeding (12 months), relative source contribution, absorption efficiency and consideration of breastmilk transfer. Central tendency, or less conservative, assumptions included: use of uncertainty factors, human half-life estimates, placental and breastmilk transfer efficiencies of PFAS, and the recommendation of individual MCLs instead of assuming toxicological equivalency among the four PFAS evaluated.

The health effects of PFAS is an evolving area of research and it is expected that future research will improve our understanding of the quantitative risks associated with PFAS. This may result in higher or lower recommendations for these and other PFAS in the future. NHDES is committed to reviewing new scientific information on PFAS to improve the understanding of this large group of chemicals and making future recommendations for evidence-based health protective drinking water standards.

Section II. Introduction

Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexanesulfonic acid (PFHxS) are individual compounds in a large class of chemicals known as perfluorinated compounds (PFCs) and more broadly as per- and polyfluoroalkyl substances (PFAS). They have been widely used since the 1940s in commercial, industrial, and household products and applications, including production of water, grease, and stain-resistant materials, fire suppression foams, non-stick cookware, wax removers, etc. (ATSDR 2018b).

All four compounds have been detected in New Hampshire's groundwater and surface water. Their widespread use, persistence and mobility in the environment and bioaccumulative properties has resulted in the detection of PFAS in blood serum in humans and animals worldwide. This has led to considerable research into their toxicity and health effects. The health effects associated with PFAS exposure are currently being researched extensively by toxicologists and epidemiologists worldwide, resulting in numerous publications being released on a continuous basis.

According to the Agency for Toxic Substances and Disease Registry (ATSDR)(ATSDR 2018b) the following health impacts may be associated with PFAS (specific compounds as noted by ATSDR):

- Hepatotoxicity - changes in certain liver enzymes in serum (PFOA, PFOS, PFHxS)
- Increases in total and LDL cholesterol levels (PFOA, PFOS, PFNA)
- Small decreases in birth weight (PFOA, PFOS)
- Endocrine system effects (PFOA, PFOS)
- Reproductive toxicity - decreased fertility (PFOA, PFOS)
- Immunotoxicity - decreased vaccine response (PFOA, PFOS, PFHxS)
- Suggestive evidence of carcinogenicity, specifically testicular and kidney cancer (PFOA, PFOS)
- Suggestive evidence of association with pregnancy-induced hypertension and/or pre-eclampsia (PFOA, PFOS)

For additional information on the toxicity and health effects of these compounds, please visit the ATSDR webpage at: https://www.atsdr.cdc.gov/pfas/health-effects.html

In addition to the ATSDR draft toxicological profile on perfluoroalkyls, several other state (NJDWQI 2017, 2018ab; MDH 2018, 2019ab; MI PFAS Science Advisory Panel 2018), federal (EPA 2016ab; NTP 2016) and international agencies (IARC 2016; Health Canada 2016ab; EFSA 2018) have reviewed the toxicological data related to PFAS and identified similar associated health impacts.

This document presents the health-based risk assessment that derived the proposed MCLs and Ambient Groundwater Quality Standards (AGQS) for these four compounds. In January 2019, NHDES released its initially proposed MCLs along with a supporting document that explained the rationale used and scientific literature reviewed to arrive at its recommendation (NHDES, 2019). The current report is not an exhaustive review of all existing studies that reference PFOA, PFOS, PFNA, PFHxS or other PFAS; rather, it is an update to the previous assessment after evaluation of newer studies and technical comments since the initial MCL proposal in January 2019 (NHDES, 2019).

Section III. Reference Dose Derivation

The U.S. EPA (2002) defines a reference dose (RfD) as:

> "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."

For PFAS, a RfD can be expressed in units of nanograms of specified PFAS (ng), per kilogram of a person's body weight (kg), per day (ng/kg-d). This allows for estimation of chemical-specific daily doses that are readily scaled to persons of differing sizes. A RfD is not the same as the minimal risk levels (MRLs) developed and used by ATSDR in that 1) MRLs are not developed with the same considerations as RfDs, and 2) MRLs are not used to define action or clean up levels for chemical contaminants (EPA 2002; ATSDR 2018a). NHDES derived RfDs for PFOA, PFOS, PFNA and PFHxS (Table 1). *Additionally, it is important to note that a RfD is a population-level value and its associated blood concentration is <u>not considered a clinically-relevant value for individuals</u>.*

Table 1. Summary of RfDs and MCLs.

Compound	Reference dose (RfD)	Exposure Assumptions	Maximum Contaminant Level (MCL)
Perfluorooctanoic acid (PFOA)	6.1 ng/kg-d	See Section IV	12 ng/L
Perfluorooctanesulfonic acid (PFOS)	3.0 ng/kg-d	See Section IV	15 ng/L
Perfluorononanoic acid (PFNA)	4.3 ng/kg-d	See Section IV	11 ng/L
Perfluorohexanesulfonic acid (PFHxS)	4.0 ng/kg-d	See Section IV	18 ng/L

Derivation of a RfD requires selection of three components (Equation 2): a point of departure (POD), uncertainty factors (UF) and, where appropriate, a dosimetric adjustment factor (DAF). The POD is based on a sensitive and human-relevant critical health effect from either animal or human studies. For PFAS, this is typically a blood concentration of a certain compound at which there is no observable adverse effect in animals (e.g. rodents). As rodents are not humans, the UF is applied to be protective by reducing the animal POD to a lower and acceptable human target serum level. The DAF then converts, by estimation, the blood concentration (ng/mL) to a body weight-adjusted (kg) amount of the chemical (ng) external to the body that would need to be ingested on a daily basis to reach the human target serum level.

$$\text{Reference dose (ng/kg/d)} = \frac{\text{Point of departure (ng/mL)}}{\text{Total uncertainty factors (unitless)}} \times \text{Dosimetric adjustment factor (mL/kg/d)}$$

As the EPA RfDs for PFOA and PFOS were deemed insufficiently protective, and there are no values for PFNA or PFHxS in the EPA Integrated Risk Information System (IRIS) database, NHDES evaluated the RfDs proposed by other agencies and derived its own values. The remainder of Section III describes how RfDs for PFOA, PFOS, PFNA and PFHxS were derived following evaluation of relevant studies and technical comments submitted to NHDES by April 12th, 2019, as well as scientific uncertainties specific to the RfDs.

Perfluorooctanoic acid or perfluorooctanoate (PFOA), CAS# 335-67-1

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFOA, NHDES recommends the critical health effect of increased relative liver weight (Loveless et al., 2006; NJDWQI 2017) as an indicator for the onset of hepatotoxicity. This is the same critical health effect previously selected in the initial MCL proposal (NHDES 2019), and based on review of the literature and technical comments received, NHDES remains confident in this recommendation.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFOA and human health impacts along with studies demonstrating toxicity in rodent models. Relative to the critical effect proposed by NHDES, there are three new studies that merit acknowledgment with regard to relative liver toxicity. This includes two studies from highly-exposed populations (Bassler et al., 2019; Nian et al., 2019) and evaluation of background exposure levels from the 2011-2014 NHANES dataset (Jain and Ducatman 2019). Bassler and colleagues (2019) reported associations between non-clinical biomarkers of hepatocyte apoptosis (cell death) as well as altered inflammatory disease of the liver with exposure to PFOA and other PFAS within a subset of subjects from the C8 Cohort (mean PFOA serum level 94.6 ng/mL). In the C8 Health Study of China (n = 1,605 participants, median PFOA serum level of 6.19 ng/mL), liver enzyme markers such as ALT and AST showed significant increases with natural log (ln)-unit changes of PFOA, other PFAS and their isomers (Nian et al., 2019). Analysis of the 2011-2014 NHANES data (n=2,883 subjects) detected consistent associations between PFAS, including PFOA, and increased ALT and GGT in obese individuals. It is noted that the cross-sectional design of certain studies and the lack of adjustments for false discovery following multiple comparisons underscore typical challenges of relying on epidemiological studies to demonstrate causal relationships, or their utility for determining the POD in RfD development. Qualitatively, these studies reinforce NHDES consideration of altered liver function and hypertrophy in rodents as a critical health effect for the basis of its PFOA RfD.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included evaluation of peer-reviewed evidence for:

- associated immunotoxicity as summarized by the National Toxicology Program (NTP 2016), ATSDR (2018b), DeWitt et al., (2012), Kirk et al., (2018) and Chang et al., (2016),
- developmental toxicity in animal models (Butenhoff et al., 2004; Lau et al., 2006; White et al., 2007; Wolf et al., 2007; Hu et al., 2010; Onishchenko et al., 2011; White et al., 2011; Albrecht et al., 2013; Cheng et al., 2013; Koustas et al., 2014; Quist et al., 2015ab; Koskela et al., 2016), associated fetal and neonatal growth impacts in humans (reviewed by Verner et al., 2015; Negri et al., 2017; Rappazzo et al., 2017; Liew et al., 2018 and ATSDR 2018b) and consideration of developmental outcomes evaluated in the U.S. EPA LHA for PFOA of 70 ng/L (EPA 2016a),
- associated human-health outcomes based on the C8 studies (Frisbee et al., 2009, 2010; Steenland et al., 2009, 2010ab, 2013; Stein et al. 2009, 2013; Lopez-Espinosa et al., 2011, 2012ab; Gallo et al., 2012; Savitz et al., 2012ab; Steenland and Woskie 2012; Barry et al., 2013; Darrow et al., 2013; Fletcher et al., 2013; Vieira et al., 2013; Watkins et al., 2013; Winquist et al., 2013; Darrow et al., 2016),

- and delayed mammary gland development in mice (White et al., 2007, 2009, 2011; Macon et al., 2011; Tucker et al., 2015).

In its initial proposal, NHDES agreed with the assessment made by the New Jersey Drinking Water Quality Institute (NJDWQI) relative to adverse effects on the liver and NHDES maintains this position. In their 2017 document, NJDWQI summarized evidence from studies in non-human primates, various strains of rodents, including PPARα knock-out mice, as well as the existing epidemiologic studies. This lead the NJDWQI to the conclusion that there was "consistency among non-occupational studies, as well as evidence of specificity, exposure-response, strength, and biological plausibility for PFOA and ALT. These findings provide evidence supporting a causal relationship between PFOA and ALT" (NJDWQI 2017). They also acknowledge the limited epidemiologic evidence, as of 2017, to definitively prove a causal relationship with PFOA and liver disease, and the available studies did not find an association. (NJDWQI 2017). While NHDES does not agree with the application of a full database uncertainty factor (NJDWQI 2018), the arguments made for consideration of hepatic effects for human health risk assessment were deemed appropriate given the existing information on PFOA.

The ATSDR 2018 draft toxicity profile for perfluoroalkyls recognized the likely associations between PFOA and hepatotoxicity (e.g., increased serum enzyme concentrations and effects on serum bilirubin) after consideration of similar epidemiological studies and the NJDWQI 2017 report (NJDWQI 2017; ATSDR 2018b). After additional review of this same document (ATSDR 2018b), NHDES agrees there is concern for the associations between exposure to PFOA and the following human health outcomes: increases in serum lipids (i.e., total and LDL cholesterol), disruption of thyroid hormone function and transport, decreased vaccine response, decreased fertility and reduced birth weight. The scientific evidence is less clear regarding other suggested human health associations and merit further investigation to establish whether these effects are truly linked to PFOA exposure. As this relates to the RfD derived by NHDES, it was determined that the animal study selected by ATSDR was not appropriate for RfD derivation following NHDES understanding of EPA methodology (EPA 2002) and was therefore not selected for use in the initial or final MCL proposal.

Regarding carcinogenicity, NHDES derived a PFOA MCL based on non-cancer endpoints. The U.S. EPA and International Agency for Research on Cancer (IARC) determined that the current evidence indicates that PFOA is a suggestive (EPA 2016) or possible (IARC 2016) carcinogen in humans. This is specific to suggestive evidence for increased risks of kidney and testicular cancer seen in rodents and mixed associations from human studies (Barry et al., 2013). Two other agencies, the USEPA (2016a) and NJDWQI (2017), have derived cancer values for PFOA using the same principal rodent study for PFOA carcinogenicity (Butenhoff et al. 2012). The U.S. EPA (2016a) and NJDWQI (2017) arrived at possible MCL values of 500 ng/L and 14 ng/L, respectively, for a one-in-a-million risk for testicular cancer. More recently, the California Office of Environmental Health Hazard Assessment (2019) has recommended a similar value of 14 ng/L for PFOA citing concern for liver damage and cancer. This discrepancy in cancer-based MCL estimates highlights the need for better information to inform cancer risk assessment for PFOA, and is expected to be an evolving area of research in years to come. Regardless of whichever is the more accurate assessment, the proposed MCL for PFOA is lower than the more conservative of these two estimates.

Determination of a point of departure

As previously proposed by NHDES (2019), the principal study and point of departure (POD) was the same study (Loveless et al., 2006) recommended and benchmark dose modeled by the NJDWQI (2017). The critical health effect was increased relative liver weight in male mice following a 14-d oral exposure to APFO (Loveless et al., 2006). There is consistent evidence for liver toxicity across wild-type and PPARα knock-out mice (Butenhoff et al., 2004; Loveless et al., 2008; Son et al., 2008; Cui et al., 2009; Elcombe et al., 2010; Yahia et al., 2010; Tan et al., 2013; Wang et al., 2015; Rebholz et al., 2016; Li et al., 2017), as well as persistent effect on liver size and structure following gestational exposure to similar dosing regimens (Quist et al., 2015). Rat studies have suggested that this effect is an adaptive response that will dissipate following cessation of the exposure to PFOA (Butenhoff et al., 2004; Hall et al., 2012). Beyond rodent models, cynomolgus monkeys display hepatic hypertrophy, increased serum triglycerides and decreased serum T_4 following chronic exposure (26 weeks) to APFO (Butenhoff et al., 2002). As it relates to the present human health risk assessment for an MCL, these effects are not entirely adaptive as animal studies suggest persistent changes in the liver following exposure during early life stages (Quist et al., 2015a). NHDES also maintains its previous position that whether the response is adaptive is not relevant to drinking water exposures as the general population should not require recovery periods from public water. Furthermore, unlike rodents that display relatively short half-lives for PFOA and other PFAS, once humans are exposed to increased levels of PFOA they will maintain elevated serum levels on a time scale of months to years. This means that brief external exposures become chronic internal doses, especially if the external dose is relatively high. The effects on liver function are considered a chronic health outcome based on the existing body of literature.

This POD is based on the benchmark dose modeling work conducted by the NJDWQI (2017) in their technical documents for their proposed RfD and MCL of 2.0 ng/kg-d and 14 ng/L, respectively, that identified a POD for PFOA of 4,351 ng/mL based on increased liver weight. NHDES did not arrive at the same RfD due to differences in the application of uncertainty factors. Differences in the final MCL are due to NH's use of the transgenerational exposure model for breastfeeding (Goeden et al., 2019).

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFOA based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As the NJDWQI (2017) derived a benchmark dose, there was no need for any additional uncertainty factors to account for lowest

observed adverse effect level (LOAEL) to no observed adverse effect level (NOAEL) conversion. As the critical effect of hepatic hypertrophy is considered the onset of the adverse effect in a sensitive model species, no additional uncertainty factor was applied to account for acute-to-chronic duration of exposure.

Although NHDES agrees with the NJDWQI selection of a critical health effect and derivation of the POD for PFOA (NJDWQI 2017), NHDES concluded there is insufficient evidence supporting the application of the more conservative full database uncertainty factor (× 10). In technical comments submitted on the initially proposed MCLs, this decision was the subject of multiple critiques. On one hand, some have argued the use of a partial uncertainty factor was under-protective as the NJDWQI applied a full factor (× 10) due to concerns for observations of delayed mammary gland development in mice exposed to PFOA during perinatal development (NJDWQI 2017, and references therein). NHDES notes that the USEPA LHA (2016a) and CDC's ATSDR draft report (2018b) did not apply any database uncertainty factor with respect to the mammary gland development studies in rodents given the lack of clarity towards human health relevance (Table 3). Similar to New Hampshire, two other state agencies, Minnesota (MDH 2018) and New York (presentation, October, 2018), derived RfDs for PFOA affording only a partial uncertainty factor for this and other adverse health impacts observed in rodent and epidemiological studies. It should be noted that both of these other agencies did not use the same POD as NJDWQI or NHDES, where Minnesota utilized a higher POD and New York utilized a lower POD compared to the benchmark dose (BMD) value from Loveless et al., (2006). Thus, NHDES believes that the application of a partial database uncertainty factor (× 3) is appropriately protective without being overly conservative given the critical health effect selected and the existing toxicological and epidemiological database.

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFOA} = \frac{4{,}351\ \text{ng/mL}}{100} = 43.5\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specified PFAS, per kg of individual body weight, per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2018, 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$DAF = V_d \times \left(\frac{Ln(2)}{t_{1/2}}\right)$$

$$DAF = 170\ mL/kg \times \left(\frac{Ln(2)}{840\ days}\right) = 1.40\times10^{-1}\ mL/kg\text{-}d$$

Consistent with the initial PFOA MCL proposal (NHDES 2019), the volume of distribution (V_d) for PFOA was 170 mL/kg (Thompson et al., 2010; EPA, 2016a). For its revised and final proposal, NHDES selected the serum half-life of 2.3 years for PFOA (Bartell et al., 2010). NHDES acknowledges that the half-life of 2.3 years is slightly less conservative than the initially proposed value for RfD derivation of 2.7 years (Li et al. 2018; NHDES 2019). This change was due, in part, to the consideration of this half-life being more appropriate given the significantly higher exposure specific to PFOA described in Bartell et al. (2010) and the larger sample size than that in Li et al. (2018).

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFOA of 6.1 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{4{,}351\ ng/mL}{100} \times 1.40\times10^{-1}\ mL/kg\text{-}d = 6.1\ ng/kg\text{-}d$$

Perfluorooctane sulfonic acid or perfluorooctane sulfonate (PFOS), CAS# 1763-23-1

Principal study & consideration of health effects

For the derivation of a RfD for PFOS, NHDES recommends the critical health effect of suppressed immunoglobulin M (IgM) production in male mice as proposed by the Minnesota Department of Health (Dong et al., 2011; MDH, 2019a). While NHDES previously proposed a RfD based on developmental toxicity, the review of existing and emerging evidence and technical comments suggest that the use of this immunotoxic endpoint represents a more appropriately cautious approach for the risk assessment of PFOS.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFOS and human health impacts along with studies demonstrating toxicity in rodent models. In the same studies that found associations between PFOA and serological markers of liver function (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019), PFOS was also associated with liver dysfunction and markers of hepatic inflammatory responses. Relative to the critical health effect selected by NHDES, one additional study on immunosuppression in humans was published since January 2019. In a prospective study of 3-month old infants from China (n = 201 participants), cord blood levels of branched isomers of PFOS were associated with reduced concentrations of antibodies towards enterovirus 71 (a causative viral agent of hand-foot-and-mouth disease; Zeng et al., 2019). Aside from hepatic and immune effects, additional studies have suggested associations between prenatal PFOS levels and early onset of puberty in girls from the Danish Birth Cohort (Ernst et al., 2019) and an estrogen-mediated relationship between cord blood levels of PFOS and birth weight (Wang et al., 2019). As with many epidemiological studies on PFAS, many of these recent studies possessed various combinations of limitations including a lack of analysis for other environmental contaminants, limited sample size and lack of analysis for the influence of breastfeeding. However, they collectively demonstrate that there is a growing body of evidence for adverse health impacts associated with PFOS.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included evaluation of peer-reviewed evidence for:

- immunotoxicity as summarized by the National Toxicology Program (NTP 2016), ATSDR (2018b) DeWitt et al., (2012) and Chang et al., (2016),
- developmental toxicity in animal models (Lau et al., 2003; Thibodeaux et al., 2003; Luebker et al., 2005ab; Yahia et al., 2008; Butenhoff et al., 2009; Onishchenko et al., 2011; Rogers et al., 2014; Wan et al., 2014), fetal and neonatal growth impacts in humans (reviewed by Verner et al., 2015; Negri et al., 2017; Rappazzo et al., 2017; Liew et al., 2018 and ATSDR 2018b) and consideration of delayed development in the U.S. EPA LHA for PFOS of 70 ng/L (EPA 2016b),
- neurobehavioral and thyroid hormone-associated effects (as reviewed by ATSDR 2018b).

NHDES acknowledges that the current understanding of the immunotoxic effects of PFOS, other PFAS and their interactions is an evolving area of research. As described by DeWitt et al. (2019), the interpretation of immunosuppression is important to consider when evaluating the relevance of associated outcomes from human studies, as well as measured responses from rodents. The current body of literature is not mature enough to clearly evaluate clinical relevance to humans, or lack thereof

(Chang et al., 2016); however, the NTP (2016) concluded that PFOS is "presumed to be an immune hazard to humans" based on animal and human data available at that time. Mouse studies indicate that PFOS impairs the T cell-dependent antibody response at low doses following sub-chronic exposure durations (Dong et al., 2009, 2011; reviewed by DeWitt et al., 2012, 2019), and was selected as the basis for a PFOS RfD by several agencies including NJDWQI (NJDWQI 2018; further detailed by Pachkowski et al. 2019), NYDOH (2018) and proposed by MDH (2019a). Although the ATSDR MRL for PFOS was based on developmental delays (Luebker et al., 2005ab), they applied an additional uncertainty factor of 10 due to the evidence for immunotoxicity (ATSDR, 2018b). Collectively, this indicates that the lower dose range at which the immunotoxic effects occur in rodents is recognized as an appropriately protective range for selection of a POD. There is a critical need for replication and use of larger study populations for understanding the immunomodulatory associations reported for PFOS and other PFAS.

NHDES derived a PFOS MCL based on non-cancer endpoints due to a lack of adequate carcinogenicity studies. IARC has not classified the carcinogenicity of PFOS at this time. The U.S. EPA determined that PFOS was a suggestive carcinogen (EPA, 2016b). This is specific to suggestive evidence for increased incidence of liver and thyroid adenomas in rats following chronic exposure. The recommendation of using non-cancer endpoints over cancer endpoints is not unique to NHDES, as other agencies have concluded that non-cancer health endpoints are adequately protective (MDH 2018; Michigan PFAS Science Advisory Panel 2018). Should additional information become available that is adequate for derivation of a cancer slope factor (CSF) for PFOS, NHDES will consider this in the framework of the MCL process.

Determination of point of departure

Following review of the technical documents deriving RfDs for PFOS based on immunosuppression in mice (NJDWQI, 2018; ATSDR 2018b; Pachkowski et al., 2019; MDH, 2019), NHDES agreed with the RfD derivation recently proposed by the Minnesota Department of Health (MDH 2019). This POD is based on serum concentrations of PFOS at the no observable adverse effect level (NOAEL) for suppressed IgM production in male mice following 60-d oral exposure (Dong et al. 2011). As summarized by MDH (2019), the critical effect reported in Dong et al. (2011) was suppressed IgM production with a NOAEL of 2,620 ng/mL (oral dose, 0.0167 mg/kg-d) and a LOAEL of 10,750 ng/mL (oral dose, 0.083 mg/kg-d). A prior study by Dong et al. (2009) reported a NOAEL of 674 ng/mL (oral dose, 0.008 mg/kg-d) for reduced plaque forming cell response to sheep red blood cells, and a similar oral LOAEL as Dong et al. (2011). However, the early work by Dong et al. (2009) did not include the intermediate dose of 0.0167 mg/kg-d that was identified as a NOAEL in their later work (Dong et al. 2011). This is further complicated as the specific effect was not replicated in both studies where plaque forming cell response was only measured in Dong et al. (2009) and IgM concentrations in the later Dong et al. (2011). As both of these metrics describe different aspects of the same immune process they do support the consideration of immunosuppression at these low doses as a POD. There remains the issue of discordance in dosing. While benchmark dose modeling of these endpoints using the original data might prove valuable to demonstrating these different metrics support a similar POD, the original data was not available for modeling and the reported data has been described as unamenable to benchmark dose modeling (NJDWQI 2018). As a result, NHDES agreed with the use of the NOAEL (2,620 ng/mL) for IgM suppression (Dong et al., 2011) instead of the lower NOAEL of 674 ng/mL (Dong et al., 2009) as a POD.

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFOS based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. The POD was based on the NOAEL described in Dong et al. (2011); thus, there was no need for additional uncertainty factors to account for LOAEL to NOAEL conversion. Dong et al. (2011) conducted a 60-day exposure so no additional uncertainty factor was applied for acute-to-chronic duration of exposure. As described by MDH (2019), an additional partial (× 3) database uncertainty factor was applied due to concerns for reports of thyroid disruption (decreased T_4) in neonatal animals and the implications of these observations in terms of neurodevelopment that has not yet been adequately studied. NHDES agreed with this consideration given the suggestive evidence for the human relevance of altered T_4 levels (reviewed by Ballesteros et al., 2017 and ATSDR, 2018b) and their potential implications for impaired neurodevelopment in humans (Grandjean and Landrigan, 2014).

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFOS} = \frac{2{,}360\ \text{ng/mL}}{100} = 23.6\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (EPA, 2016ab; NJDWQI, 2017, 2018a; ATSDR, 2018b; MDH, 2018, 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$DAF = V_d \times \left(\frac{Ln(2)}{t_{1/2}}\right)$$

$$DAF = 230\ mL/kg \times \left(\frac{Ln(2)}{1{,}241\ days}\right) = 1.28\times10^{-1}\ mL/kg\text{-}d$$

Consistent with the initial PFOS MCL proposal (NHDES 2019), the V_d for PFOS was 230 mL/kg (Thompson et al., 2010). In its revised and final proposal, NHDES maintains its use of a 3.4-year half-life estimate based on the average across men and women, described in Li et al. (2018; NHDES 2019). NHDES considered the longer half-life values reported for retired fluorochemical workers (Olsen et al. 2007), and deemed these to be inappropriately conservative given the use of the Minnesota transgenerational model for exposure assessment which emphasizes early-life and breastfeeding exposures.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFOS of 3.0 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{2{,}360\ ng/mL}{100} \times 1.28\times10^{-1}\ mL/kg\text{-}d = 3.0\ ng/kg\text{-}d$$

Perfluorononanoic acid or perfluorononanoate (PFNA), CAS# 375-95-1

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFNA, NHDES recommends the critical health effect of increased relative liver weight in pregnant mice (Das et al., 2015; NJDWQI, 2018) as an indicator for the onset of hepatotoxicity. This is the same critical health effect previously selected in the initial MCL proposal (NHDES, 2019), and based on additional review of the literature NHDES remains confident in this decision.

Since the initial MCL proposal by NHDES at the start of January 2019, additional studies have been published related to associations between PFNA and associated human health impacts along with studies demonstrating toxicity in rodent models. In the same studies that found associations between PFOA and serological markers of liver function (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019), PFNA was also associated with liver dysfunction and markers of hepatic inflammatory responses. As discussed later, this co-association between multiple PFAS and the same health outcomes is acknowledged as a present challenge of epidemiological research. The same study of the Danish Birth Cohort that associated PFOS with an early onset of puberty in girls found that prenatal serum levels of PFNA were associated with delayed onset of puberty in boys (Ernst et al., 2019). Ernst and colleagues (2019) noted that these associations merit caution in their interpretation and require replication due to their novelty. Unlike PFOA and PFOS, PFNA has been the subject of relatively less research and its lower background serum concentrations compared to PFOA and PFOS present a challenge to identifying its effects in human populations.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). At the time, two major documents reviewed the toxicity of PFNA in humans and rodents (NJDWQI, 2018; ATSDR, 2018b). As noted in both documents, relatively little research has been conducted on PFNA despite its historical use and presence in a variety of environmental media. The NJDWQI concluded there was limited evidence associating PFNA with changes in serum ALT as a biomarker of hepatotoxicity (NJDWQI, 2018), whereas the ATSDR determined these inconsistencies in epidemiological data did not merit inclusion of hepatotoxicity as an associated health outcome for PFNA (ATSDR, 2018b). In its initial proposal, NHDES agreed with the assessment made by the NJDWQI relative to adverse effects on the liver and NHDES maintains this position. Given the limited amount of epidemiological data currently available for PFNA and its similarity in chemical structure to PFOA and biological activities in animal models, NHDES determined that the associated hepatotoxic effects were more relevant and sensitive for human health risk assessment than the developmental and endocrine effects reported in animal studies. While NHDES does not agree with the application of the database uncertainty factor or animal-to-human dose extrapolation, the arguments made for consideration of hepatotoxicity by NJDWQI (2018) were deemed appropriate given the existing information.

To date, the carcinogenicity of PFNA has not been reported in a rodent model. The human carcinogenicity of PFNA has not been classified by the U.S. EPA, IARC or CDC (ATSDR). Therefore, NHDES did not conduct a cancer-based risk assessment for PFNA. Should additional information become available that is adequate for consideration of a cancer slope factor (CSF) for PFNA, NHDES recommends consideration as to whether its development and application of such values would be more protective than the proposed MCL.

Determination of a point of departure

As previously proposed by NHDES (2019), the principal study and point of departure (POD) was the same study (Das et al., 2015) recommended and benchmark dose modeled by the NJDWQI (2018). The critical health effect was increased relative liver weight in pregnant mice following a 17-d (duration of gestation) oral exposure to PFNA (Das et al., 2015). The internal LOAEL for these mice was 12,400 ng/mL which corresponded to an oral dose of 1.0 mg/kg-d (Das et al., 2015). While no significant mortality was observed at this dose, higher oral doses (>5.0 mg/kg-d) were associated with neonatal mortality in mice. Wolf et al. (2010) demonstrated the profound effects of PFNA on mouse pups were due to PPARα activation which raises uncertainty about the qualitative and quantitative relevance of this outcome to human health. Additional studies demonstrate that rodent models display hepatotoxic responses towards PFNA (Wolf et al., 2010; Wang et al., 2015), with evidence of PPARα-independent mechanisms (Rosen et al., 2017).

This POD is based on the benchmark dose modeling work conducted by the NJDWQI (2018) in their technical documents for their proposed MCL of 13 ng/L. It should be noted that NJDWQI did not derive a RfD as a part of the MCL development, as a ratio method was used instead of a DAF with water ingestion rate to convert the target serum level to a corresponding water concentration. NHDES did not arrive at the same MCL because NHDES opted to derive a RfD consistent with the other PFAS evaluated, as well as use of the transgenerational exposure model for breastfeeding (Goeden et al., 2019; MIDHHS, 2019).

Application of uncertainty factors

A total uncertainty factor of 100 was applied to the POD for PFNA based on:

Intraspecies variability (10) × Interspecies variability (3) × Database limitations (3) = 100

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 is rounded to 100 from 99.982.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As the NJDWQI (2018) derived a benchmark dose, there was no need for any additional uncertainty factors to account for LOAEL to NOAEL conversion. As with PFOA, the critical effect of hepatic hypertrophy is considered the onset of the adverse effect in a sensitive model species. Consistent with PFOA, no additional uncertainty factor was applied to account for acute-to-chronic duration of exposure. The NJDWQI applied a full LOAEL to NOAEL uncertainty factor (× 10) to account for differences between the 17-d exposure in Das et al. (2015) and longer exposures resulting in reported adverse effects (summarized in NJDWQI, 2018). As increased liver weight in mice is already considered to be a highly-sensitive critical effect in response to PFAS, NHDES determined this was overly conservative given similar uncertainty factor considerations for the similar perfluorinated carboxylic acid, PFOA.

In its original proposal, NHDES applied a full database uncertainty factor (× 10) to account for the limited existing literature on PFNA (× 3), as well as the absence of a serum-derived human half-life estimate (× 3; NHDES 2019). As a part of its revision to the proposed RfDs and subsequent MCLs, NHDES utilized the more conservative half-life of PFNA derived for men and older women. Given the application of this more conservative half-life estimate, NHDES removed the associated partial uncertainty factor for PFNA. NHDES retained the partial uncertainty factor of × 3 to account for a lack of multigenerational rodent studies using PFNA, as well as concern for potential immunotoxic impacts seen with other PFAS (NTP 2016; DeWitt et al., 2012, 2019).

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFNA} = \frac{4{,}900\ \text{ng/mL}}{100} = 49.0\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$\text{DAF} = V_d \times \left(\frac{\text{Ln}(2)}{t_{1/2}}\right)$$

$$\text{DAF} = 200\ \text{mL/kg} \times \left(\frac{\text{Ln}(2)}{1{,}570\ \text{days}}\right) = 8.83 \times 10^{-2}\ \text{mL/kg-d}$$

Consistent with the initial PFNA MCL proposal (NHDES 2019), the V_d for PFNA was 200 mL/kg based on similar assumptions made by ATSDR (ATSDR 2018b). In this revised proposal, NHDES adjusted the half-life value from 2.5 to 4.3 years based on urinary half-lives estimated for men and older women, groups that tend to eliminate PFAS slower than younger and reproductive age women (Zhang et al., 2013; NHDES, 2019). As previously discussed in its initial proposal (NHDES, 2019), NHDES would prefer to have more reliable serum half-life estimates for PFNA instead of the urinary-derived estimates reported by Zhang and colleagues (2013). However, since the submission of the initial proposal no additional studies have been published that report a serum-based estimate for the half-life of PFNA in humans. Should additional peer-reviewed studies emerge that provide more rigorous estimates of these values, NHDES recommends consideration as to whether such data would represent and merit a significant change for the PFNA RfD.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFNA of 4.3 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{4{,}900\ \text{ng/mL}}{100} \times 8.83\times10^{-2}\ \text{mL/kg-d} = 4.3\ \text{ng/kg-d}$$

Perfluorohexane sulfonic acid or perfluorohexane sulfonate (PFHxS), CAS# 355-46-4

Principal study & consideration of health effects

For the derivation of a RfD and MCL for PFHxS, NHDES recommends the critical health effect of impaired female reproduction as determined by reduced litter size initially reported in Chang et al. (2018). This RfD derivation is currently under peer-review with a scientific journal (Ali et al. *in review*). This is the same critical health effect previously proposed in the initial MCL proposal (NHDES 2019), albeit the present value is adjusted for benchmark dose modeling and selection of endpoint specific factors for dosimetric adjustment. NHDES developed the revised RfD in collaboration with external collaborators, Dr.'s Leah Stuchal and Stephen Roberts at the University of Florida, and awaits external peer-review on the soundness of its derivation. Should peer-review recommend revision and adjustment of the proposed RfD, NHDES will review the current MCL to determine if adjustments are required to be adequately protective of human health.

Since its initial proposal (NHDES, 2019), there has been a limited amount of new information generated relative to PFHxS. The Minnesota Department of Health proposed a RfD for PFHxS of 9.7 ng/kg-d based on reduced free T_4 in exposed rats using unpublished data from the NTP. At the time of writing this recommendation, the ATSDR has not released a revision to their 2018 draft MRL of 20 ng/kg-d based upon thyroid follicular cell damage in rats (ATSDR, 2018b). PFHxS showed similar associations with serological markers of liver function and inflammation as reported for PFOA, PFOS and PFNA (Nian et al., 2019; Jain and Ducatman, 2019; Bassler et al., 2019). Despite its legacy of widespread environmental occurrence associated primarily with AFFF use and growing regulatory interests, relatively little new toxicological information has emerged for PFHxS as of June 2019.

Studies published prior to 2019 were considered as a part of the initial PFAS MCL proposal put forward by NHDES (2019). This included re-evaluation of peer-reviewed evidence considered by ATSDR (2018b) including:

- thyroid toxicity including altered thyroid histology and reduced T_4 levels in rodent models (Butenhoff et al., 2008; Chang et al., 2018; Ramhøj et al., 2018), as well as epidemiology studies for altered T_4 levels (Ballesteros et al., 2017),
- immunomodulation in humans (Grandjean et al., 2012; Dong et al., 2013; Humblet et al., 2014; Okada et al., 2014; Buser and Scinicariello 2016; Stein et al., 2016; Zhu et al., 2016)
- reproductive and developmental toxicity in rodents (Butenhoff et al., 2008; Viberg et al., 2013; Chang et al., 2018; Ramhøj et al., 2018)
- hepatotoxicity or changes in lipid metabolism in rodents (Butenhoff et al., 2008; Bijland et al., 2011; Rosen et al., 2017; Chang et al., 2018; Ramhøj et al., 2018) and humans (Nelson et al., 2010; Starling et al., 2014; Mattsson et al. 2015).
- and human carcinogenicity (Hardell et al., 2010; Bonefel et al., 2014; Hurley et al., 2018).

To date, the carcinogenicity of PFHxS has not been reported in a rodent model. The human carcinogenicity of PFHxS has not been classified by the U.S. EPA, IARC or CDC (ATSDR). Therefore, NHDES did not conduct a cancer-based risk assessment for PFHxS. Should additional information become available that is adequate for consideration of a CSF for PFHxS, NHDES recommends consideration as to whether its development and application would be more protective than the proposed MCL.

Determination of a point of departure

As described in its initial MCL proposal (NHDES 2019), the principal study and point of departure (POD) was the same study (Chang et al., 2018) that has been adjusted primarily by use of benchmark dose modeling (Ali et al., *in review*). The critical health effect was reduced litter size in mice following a 14-d, prior to pregnancy, oral exposure to PFHxS (Chang et al., 2018). As mentioned above, the details and methodology for derivation of the POD for PFHxS are currently under review in Ali et al (*in review*). Benchmark dose (BMD) modeling was performed using Benchmark Dose Software (BMDS) (Version 3.1; USEPA, 2019). The critical effect endpoint was a change in the mean live litter size for adult CD-1 female mice, and due to the unavailability of litter-specific data was modeled based on PFHxS serum concentrations on study day 14 (reported in Chang et al., 2018). This resulted in a benchmark dose of 41,200 ng/mL and a 95% lower confidence limit on the benchmark dose (BMDL) of 13,900 ng/mL. NHDES determined that this is an appropriately cautious endpoint given the limited number of animal studies (reviewed in NHDES, 2019), considerably longer half-lives of PFHxS in humans when compared to other PFAS (Olsen et al., 2007; Zhang et al., 2013; Worley et al., 2017; Li et al., 2018), environmental occurrence and exposures (Daly et al., 2018), as well as suggestive associations of reproductive impacts in humans (Vélez et al., 2015; Zhou et al., 2017; Zhang et al., 2018).

Application of uncertainty factors

A total uncertainty factor of 300 was applied to the POD for PFHxS based on:

Intraspecies variability (10) × Interspecies variability (3) × Duration of exposure (3) × Database limitations (3) = 300

For the non-risk assessor, the units of 3 and 10 are for partial (half) and full log units. So, a full log unit of 10 equals 10^1, but a half log unit of $10^{½}$ or $10^{0.5}$ is equal to 3.162. As a convention of risk assessment using EPA methodology (EPA 2002), the value of 3.162 is presented as 3. Thus, 10 × 3 × 3 × 3 is rounded to 300 from 316.14.

The full factor of 10 for intraspecies variability was deemed appropriate to protect for the poorly characterized differences in toxico-dynamics (× 3) and -kinetics (× 3) within the human population. As NHDES applied a DAF to convert the rodent serum concentration to an oral human dose, only a partial uncertainty factor (× 3) was applied for interspecies variability. As benchmark dose modeling was used to derive a POD, detailed in Ali et al. (*in review*), there was no need for any additional uncertainty factors to account for LOAEL to NOAEL conversion. After careful evaluation of technical comments and re-assessment of the literature and principal study, an additional but partial uncertainty factor (× 3) was applied to account for acute-to-chronic duration of exposure of female mice. In Chang et al. (2018), female mice received a less than chronic exposure (14 days) to PFHxS prior to the start of pregnancy. Because of the relatively limited number of studies on PFHxS and evidence for adverse impacts following longer exposure to similar compounds (i.e., PFOS), this was determined to be appropriate without being overly conservative (e.g., a full factor of × 10).

In its original proposal, NHDES applied a full database uncertainty factor (× 10) to account for the limited existing literature on PFHxS (× 3), as well as associations with thyroid hormone and transport interference (× 3; NHDES 2019). As a part of its revision to the proposed RfD and subsequent MCL,

NHDES determined the existing single-generation studies provide some basis for evaluating the reproductive and developmental toxicity of PFHxS. However, NHDES retained a partial uncertainty factor (× 3) to account for a lack of multigenerational rodent studies, as well as concern for potential immunotoxic impacts seen with other PFAS that have yet to be assessed (NTP 2016; DeWitt et al., 2019). The protracted human half-life of PFHxS relative to other PFAS underscores the need for additional research into biological impacts following chronic exposures.

Estimation of a human equivalent oral dose

The POD represents an internal animal serum level associated with the adverse health outcome of concern. Dividing the POD by the total uncertainty factor yields a protective target serum level equivalent for the human population. *This is not a clinical or diagnostic value, nor should it be interpreted as such*.

$$\text{Target serum level for PFHxS} = \frac{13{,}900\ \text{ng/mL}}{300} = 46.3\ \text{ng/mL}$$

To estimate how this internal blood level corresponds to an external oral dose of the specified compound, a dosimetric adjustment factor is applied by multiplication to identify a dose in ng of specific PFAS per kg of individual body weight per day (ng/kg-d). This step accounts for the highly-bioaccumulative nature and unique half-life estimates of each compound, and is consistent with prior risk assessment methods for derivation of RfDs for PFAS (USEPA 2016ab; NJDWQI 2017, 2018a; ATSDR 2018b; MDH 2019ab). The human equivalent oral dose is estimated by the following equations:

$$\text{Reference dose (RfD)} = \frac{\text{Point of departure (POD)}}{\text{Total uncertainty factors (UF)}} \times \text{Dosimetric adjustment factor (DAF)}$$

Where the DAF is equal to,

$$\text{DAF} = V_d \times \left(\frac{\text{Ln}(2)}{t_{1/2}}\right)$$

$$\text{DAF} = 213\ \text{mL/kg} \times \left(\frac{\text{Ln}(2)}{1{,}716\ \text{days}}\right) = 8.61\times10^{-2}\ \text{mL/kg-d}$$

In its revised MCL proposal for PFHxS, NHDES has changed both the V_d and half-life estimate for PFHxS to reflect the female-specific health impact utilized as the basis of the RfD. The V_d for PFHxS was reduced from 287 to 213 mL/kg which reflects a female-specific V_d value for PFHxS (Sundström et al., 2012). Sundström et al. (2012) reports the volume of distribution for cynomolgus monkeys, not humans, and no human V_d is currently available for PFHxS. Similar to ATSDR (ATSDR 2018b) and other agencies (MDH 2019b; MIDHHS 2019), NHDES used the non-human primate value as an estimate for the human volume of distribution. Similarly, NHDES adjusted the half-life value from 5.3 to the female-specific estimate of 4.7 years (average) based on a study of a community exposed to PFHxS through contaminated drinking water (Li et al. 2018; discussed in NHDES 2019). It is noted that use of this average half-life estimate for women is less conservative than longer average half-life estimates of 8.5 years (Olsen et al., 2007) or 7.4 years (Li et al., 2018) that rely on serum levels in men, or longer estimates of 7.7-35 years for women depending on age (Zhang et al., 2013). However, given the conservative nature and sex-specific effect selected for the POD of PFHxS, the use of a 4.7-year half-life in women was deemed appropriate without being overly-conservative.

Thus, using this chemical-specific DAF and the aforementioned point of departure and uncertainty factors, NHDES derived an oral reference dose for PFHxS of 4.0 ng/kg-d.

$$\text{Reference dose (RfD)} = \frac{13{,}900\ \text{ng/mL}}{300} \times 8.61\times10^{-2}\ \text{mL/kg-d} = 4.0\ \text{ng/kg-d}$$

Summary of Recommended RfDs for PFOA, PFOS, PFNA and PFHxS

Recommended RfDs

NHDES recommends the following chronic oral RfDs for PFOA, PFOS, PFNA and PFHxS:

- PFOA, 6.1 ng/kg-d
- PFOS, 3.0 ng/kg-d
- PFNA, 4.3 ng/kg-d
- PFHxS, 4.0 ng/kg-d

These RfDs are for protection from the primary health effects of liver toxicity (PFOA and PFNA), immune suppression of antibody responses (PFOS) and reduced female fertility (PFHxS) based on evidence from animal studies. In addition to these primary health outcomes, these RfDs are expected to be reasonably protective for associated and secondary (less sensitive) health outcomes that occur at similar or higher serum concentrations in rodents. Secondary health effects for these and other PFAS include disruption of thyroid and sex hormone levels and their signaling, teratogenic effects, early-life growth delays, changes in cholesterol levels, neurobehavioral effects, renal toxicity and fertility in rodent models. NHDES believes its selection of PODs, uncertainty factors and DAFs for each RfD provides adequate protection of human health from appreciable risk of these primary and secondary health effects during a lifetime.

Table 2 presents the NHDES recommended RfDs or MRLs, along with their applied uncertainty factors those selected by other agencies that have evaluated these same PFAS. The application of uncertainty factors follows EPA guidance (EPA 2002), and is dependent on the principal study selected and consideration of other available studies. However, it is not uncommon for different risk assessors and toxicologists to arrive at different applications of uncertainty factors when considering where reasonable and health-protective conservatism is being applied in the risk assessment process.

Discussion of scientific uncertainties

While the human health effects of PFAS is a rapidly growing area of scientific research, the exact nature of their associated health effects in humans remains uncertain (ATSDR, 2018b; Michigan Panel, 2018). The cross-sectional nature of most epidemiological studies precludes proof of causality between measured PFAS serum concentrations and the reported associated health outcomes. This is especially problematic as the extraordinarily long half-lives of PFAS (years) make it difficult to disentangle the associated health effects in these studies from co-exposure to other environmental contaminants with relatively shorter half-lives (days to weeks). Additionally, there is a general lack of true control groups for comparison as various combinations of PFAS are detectable in the blood of virtually all populations from around the world. There is concern for the implications of reverse causation with certain health outcomes associated to PFAS. As an evolving area of scientific research, NHDES anticipates new findings will improve the understanding of PFAS-related health effects in humans.

Due to the limitations of epidemiological studies, RfDs were derived using animal data. There are inherent uncertainties associated with RfDs derived from animal studies (EPA 2002), specifically related

to considerations of human health relevance (e.g., biological plausibility) and translation of animal findings to human equivalent values (i.e., uncertainty factors and DAFs).

As a part of its initial proposal (NHDES, 2019), NHDES considered the contentious issue of peroxisome proliferator-activated receptor subtype α (PPARα) activation in rodents and its relevance to human health. The activation of PPARα is a contributing pathway for several of the reported toxic responses in rodent models evidenced by genetic knockout studies and gene expression profiling studies (reviewed by ATSDR 2018b and NHDES 2019). This is especially true for hepatotoxicity and changes in lipid metabolism in rodents following exposure to PFAS due to upregulation of rodent specific pathways leading to oxidative stress (Perkins et al., 2004; Loveless et al., 2006; Rosen et al., 2007, 2008, 2017; Das et al., 2017; reviewed by ATSDR, 2018b). *In vitro* testing demonstrates that PFAS show a stronger binding affinity for rodent PPARα when compared to human PPARα (Wolf et al., 2008). These and other studies reviewed by NHDES (2019) suggest qualitative and quantitative differences in toxicity between species for PPARα-dependent effects.

Such qualitative and quantitative differences raise concern for selection of critical health effects such as liver toxicity based on rodent studies (reviewed by Klaunig et al., 2012), and have been a major criticism of the half-lives derived by NHDES and other agencies for RfDs for PFOA, PFOS, PFNA and PFHxS. Based on existing toxicological information, NHDES contends that selected critical effects from animal studies are appropriate for the protection of human health. While the physiological roles of PPARs (i.e., PPARα, β and γ) in humans are less defined than those of the other nuclear receptors like the estrogen or androgen receptor, there is evidence that they are involved in lipid metabolism (Issemann and Green, 1990; Lee et al., 1995) and function of muscle, adipose and immune cells throughout the body (Tyagi et al., 2011). Independent of PPARα activation, there is evidence for other mechanisms for rodent toxicity (e.g. mitochondrial dysfunction) that are potentially relevant to humans and other organisms (Hagenaars et al., 2013; Cui et al., 2015; reviewed by Li et al., 2017; Li et al., 2018; NHDES, 2019). Furthermore, evidence from non-human primates further suggest that effects on the liver, cholesterol levels, thyroid hormones and the immune system are relevant to humans and not isolated to rodent studies (Griffith and Long 1980; Thomford 2001; Butenhoff et al., 2002; Seacat et al., 2002). Taken collectively, this supports the NHDES risk assessment and derivation of RfDs using the selected critical health effects.

With respect to uncertainty factors, NHDES received multiple comments regarding its application of uncertainty factors in the initially proposed MCLs (NHDES, 2019). Table 2 presents the uncertainty factors used by other state or federal agencies for the derivation of RfDs for PFOA, PFOS, PFNA or PFHxS, and demonstrates that NHDES's selections are within the norms of the professional practice. As previously explained for each compound, NHDES considered available information from human and animal studies to arrive at the total uncertainty factors applied for each RfD. Difference in principal study selection and consideration of available data results in differences in the selection and application of total uncertainty factors (EPA 2002). Given the selection of principal studies and considerations of exposure assumptions described in Section IV, NHDES remains confident that its application of uncertainty factors is appropriate without being overly conservative.

Table 2. Interagency Differences in Uncertainty Factors. Summary of uncertainty factor allocations, RfDs and MRLs by government risk assessment groups.

Specific Uncertainty Factors	ATSDR[a] (MRLs)	US EPA[b,c] (RfD)	TX CEQ[d] (RfD)	MN DOH[e-g] (RfD)	NJ DWQI[h-j] (RfD)	NH DES (RfD)	NY DOH[k] (RfD)
PFOA							
Principal Study	Koskela et al. 2016	Lau et al. 2006	Macon et al. 2011	Lau et al. 2006	Loveless et al. 2006	Loveless et al. 2006	Macon et al. 2011
Human Variability	10	10	10	10	10	10	10
Interspecies Differences	3	3	1	3	3	3	3
Duration of Exposure	1	1	1	1	1	1	1
LOAEL to NOAEL	10	10	30	1	1	1	1
Database Insufficiency	1	1	1	3	10	3	3
Total Uncertainty Factor	300	300	300	100	300	100	100
RfD (ng/kg-d)	3.0	20.0	12.0	18.0	2.0	6.1	1.5
PFOS							
Principal Study	Luebker et al. 2005	Luebker et al. 2005	Zeng et al. 2011	Dong et al. 2011	Dong et al. 2009	Dong et al. 2011	Dong et al. 2009
Human Variability	10	10	10	10	10	10	10
Interspecies Differences	3	3	1	3	3	3	3
Duration of Exposure	1	1	1	1	1	1	1
LOAEL to NOAEL	1	1	10	1	1	1	1
Database Insufficiency	10	10	1	3	1	3	1
Total Uncertainty Factor	300	300	100	100	30	100	30
RfD (ng/kg-d)	2.0	20.0	23.0	3.0	1.8	3.0	1.8
PFNA							
Principal Study	Das et al. 2015	n.a.	Fang et al. 2010	n.a.	Das et al. 2015	Das et al. 2015	n.a.
Human Variability	10	-	10	-	10	10	-
Interspecies Differences	3	-	1	-	3	3	-
Duration of Exposure	1	-	10	-	10	1	-
LOAEL to NOAEL	1	-	1	-	1	1	-
Database Insufficiency	10	-	10	-	3	3	-
Total Uncertainty Factor	300	-	1,000	-	1,000	100	-
RfD (ng/kg-d)	3.0		12.0		0.73	4.3	
PFHxS							
Principal Study	Butenhoff et al. 2009	n.a.	Hoberman & York 2003	Unpublished NTP data	n.a.	Chang et al. 2018	n.a.
Human Variability	10	-	10	10	-	10	-
Interspecies Differences	3	-	1	3	-	3	-
Duration of Exposure	1	-	1	1	-	3	-
LOAEL to NOAEL	1	-	3	1	-	1	-
Database Insufficiency	10	-	10	10	-	3	-
Total Uncertainty Factor	300	-	300	300	-	300	-
RfD (ng/kg-d)	20.0		3.8	9.7		4.0	

n.a. indicates the specific compound was not assessed or reported on by the specific agency.
[a] ATSDR, 2018b. Draft Toxicological Profile for Perfluoroalkyls
[b] U.S. EPA, 2016a. Health Effects Support Document for Perfluorooctanoic Acid (PFOA)
[c] U.S. EPA, 2016b. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)
[d] TX Commission on Environmental Quality (TXCEQ), 2016. Perfluoro Compounds (PFCs): available at: https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf
[e] Minnesota Department of Health (MDH), 2018. Toxicological Summary for: Perfluorooctanoate.
[f] Minnesota Department of Health (MDH), 2019a. Toxicological Summary for: Perfluorooctane sulfonate.
[g] Minnesota Department of Health (MDH), 2019b. Toxicological Summary for: Perfluorohexane sulfonate.

[h] New Jersey Drinking Water Quality Institute (NJDWQI), 2017. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA)
[i] New Jersey Drinking Water Quality Institute (NJDWQI), 2018a. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS)
[j] New Jersey Drinking Water Quality Institute (NJDWQI), 2018b. Appendix A: Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA)
[k] New York Department of Health (NYDOH), 2018 and personal communications. Presentation available at: https://www.health.ny.gov/environmental/water/drinking/dwqc/

Section IV. Drinking Water Exposure Assumptions, Modeling and Resulting MCLs

Using the reference dose (RfD) derived in Section III, the MCL considers the estimated daily intake of water from a specific source and how much drinking water contributes to the total exposure from all other sources of a specified contaminant. Specific methodologies for deriving health protective water criteria are detailed by the EPA (USEPA 1989, 2004, 2017, 2018). Although NHDES chose a different approach, the conventional method for deriving drinking water values utilizes the following equation:

$$\text{Maximum contaminant level (ng/L)} = \frac{\text{Reference dose (ng/kg-d)}}{\text{Daily water ingestion rate (L/kg-d)}} \times \text{Relative source contribution (unitless)}$$

For a simple example, a drinking water value for PFOA using the currently recommended RfD, 95th percentile ingestion rate of lactating women and a relative source contribution of 0.5 (meaning 50%) is shown below. This approach was used in the initially proposed MCL, but is not being applied following consideration of breastfeeding (Goeden et al., 2019).

$$\text{Example for PFOA (not an actual MCL recommendation by NHDES)} = \frac{6.1\ \text{ng/kg-d}}{0.055\ \text{L/kg-d}} \times 0.5 = 55\ \text{ng/L}$$

The daily water ingestion rate is a body-weight adjusted factor specific to certain age groups, to gender, and to lactation or pregnancy status. In its initial proposal, NHDES selected the water ingestion rate of the 95th percentile of lactating women, an estimated value of 0.055 L/kg-d (EPA, 2011; NHDES, 2019). While lower estimates are more reflective of the central tendencies of the general population, especially non-lactating women, they were deemed inadequately protective for the larger population. The values are selected from the Exposure Factors Handbook (EPA 2011), which was recently updated specifically for these ingestion rates (see Chapter 3 of EPA, 2019). These updated values were used by NHDES.

Instead of applying a fixed daily water ingestion rate that is assumed to be protective across a lifespan, NHDES applied the toxicokinetic model described by Goeden et al. (2019) to consider how changes in water ingestion at a given MCL are predicted to influence internal blood levels of each PFAS. This is due to the prolonged and elevated internal doses (i.e., serum levels) predicted across infancy and childhood resulting from PFAS in breastmilk. NHDES acknowledges that this is a departure from typical methodology for deriving such a standard, but the unique properties of PFAS (i.e., long half-lives) merit its application to be truly protective across all life stages for the chronic health impacts associated with these chemicals.

The relative source contribution (RSC) is an estimate of how much of the typical daily exposure will be allowed to come from drinking water. EPA recommends an RSC floor of 20% of the RfD and a ceiling of 80% of the RfD. The intention of an RSC ceiling of 80% is to ensure that total exposure from all sources does not exceed 100% of the RfD with a margin of safety for potential unknown or underestimated exposures. PFAS are present in a wide variety of environmental media (Moriwaki et al., 2003; Trudel et al., 2008; Haug 2011; Haug et al., 2011; Winkens et al., 2017, 2018) and consumer products (Haug 2011; Carpet and Textile Treatment - Washburn et al., 2005; Winkens et al. 2017; Cosmetics - Kang et al., 2016; Fast Food Packaging – Schaider et al., 2017), with an ever-growing number of potential sources identified (Boronow et al., 2019; Kim et al., 2019; Nakayama et al., 2019). Thus, for the typical person, it is unlikely that drinking water is responsible for 100% of their exposure. However, an exact profile for the proportions of exposure from various sources remains poorly characterized. The latter part of this section details how this was evaluated by NHDES to arrive at a RSC of 50% for PFOA, PFOS, PFNA and PFHxS.

Application of Goeden et al. (2019) for exposure modeling

As a part of the evaluation of published research and technical comments on the initially proposed MCLs (NHDES, 2019), NHDES has adopted the use of the transgenerational toxicokinetic model (detailed in Goeden et al., 2019), for the determination of appropriately protective health-based MCLs. This is a toxicokinetic model that predicts the serum concentration of PFAS due to drinking water exposure and consumption of breastmilk or formula across a lifespan starting at birth (Goeden et al., 2019). It does not predict an effect (health outcome) due to exposure from drinking water, only the blood concentration for an individual in a reasonable maximum exposure (RME) scenario. The tolerable blood concentration in the RME scenario, or threshold, is determined by the chemical-specific RfD and RSC. This Excel-based model is available upon request from the MN Department of Health.

After review of the model and studies on the placental transfer (Fei et al., 2007; Midasch et al., 2007; Monroy et al., 2008; Fromme et al., 2010; Beesoon et al., 2011; Kim et al., 2011; Liu et al., 2011; Needham et al., 2011; Lee et al., 2013; Porpora et al., 2013; Zhang et al., 2013; Kato et al., 2014; Cariou et al., 2015; Manzano-Salgado et al., 2015; Fisher et al., 2016; Yang et al., 2016; Chen et al., 2017; Mamsen et al., 2019) and breastmilk transfer (Karrman et al., 2007; Haug et al., 2011; Kim et al., 2011; Liu et al., 2011; Cariou et al., 2015; Gyllenhammer et al., 2018) of PFOA, PFOS, PFNA and PFHxS, NHDES determined this novel and "fit-for-purpose" tool (Goeden et al., 2019) was necessary to evaluate exposure outcomes from the proposed MCLs. Specifically, the transfer of PFAS into breastmilk combined with the relatively high breastmilk and water ingestion rates of infants results in a prolonged elevation of serum levels throughout childhood. Under RME assumptions, the serum levels are predicted to be drastically higher than background serum levels seen in the general population, which is assumed to be free of widespread PFAS contamination in drinking water. Furthermore, this elevation throughout childhood into late adolescence limits the RSC allotment for exposure to other sources of PFAS in the environment that, to date, are not regulated.

The following subsections describe the inputs selected by NHDES for RME modeling using Goeden et al. (2019). A summary of model inputs, and associated references, used by NHDES for selection of the proposed MCLs are provided in Table 3.

Human half-life and V_d assumptions

Explanations of the selected half-lives for PFOA, PFOS, PFNA and PFHxS are described in the discussions of DAFs in Section III of this report. For PFOA, an average serum-based half-life was selected from Bartell et al. (2010), which was estimated from a sample population of 200 individuals from the Mid-Ohio valley who were exposed to PFOA from their drinking water supply due to contamination from a DuPont facility. NHDES selected the half-life estimates from Li et al. (2018) for PFOS and PFHxS. These serum-derived half-life estimates were determined to be more representative of the general population, and were obtained from a Swedish community (n = 106 participants) exposed to PFAS, namely PFOS and PFHxS, from drinking water contaminated by AFFF use at a nearby airbase (Li et al., 2018). Finally, the half-life estimate for PFNA was selected from Zhang et al. (2013) which reports urine-based values from a Chinese population (n = 86 participants).

Similar to the half-life values, the volume of distribution (V_d) estimates were identical to those selected by NHDES to derive RfDs for PFOA, PFOS, PFNA and PFHxS (Section III, and references therein).

Table 3. Exposure Model Parameters. Summary of parameters utilized in the transgenerational model (Goeden et al., 2019) by NHDES for derivation of proposed MCLs.

Model Parameter	Central or Upper Tendency of Parameter	PFOA	PFOS	PFHxS	PFNA
Half-Life, years (yrs)	Central	2.3 [a]	3.4 [b]	4.7 [b]	4.3 [c]
Placental Transfer Ratio	Central	0.72 [d]	0.40 [d]	0.70 [d]	0.69 [e]
Breastmilk Transfer Ratio	Central	0.050 [d]	0.017 [d]	0.014 [d]	0.032 [e]
Volume of Distribution (V_d), L/kg	Central	0.170 [f]	0.230 [f]	0.213 [g]	0.200 [e,h]
Relative Source Contribution (RSC), %	Central	50	50	50	50
		Same for All 4 PFAS Exposure Scenario Models			
Duration of Exclusive Breastfeeding, months	Upper	12			
Water Ingestion Rates, mL/kg-d [i] (EPA Exposure Factors Handbook, 2019 Update)					
Birth to <1 mon	Upper	224			
1 to <3 mons	Upper	267			
3 to <6 mons	Upper	158			
6 to <11 mons	Upper	133			
1 to <2 yrs	Upper	57			
2 to <3 yrs	Upper	67			
3 to <6 yrs	Upper	45			
6 to <11 yrs	Upper	41			
11 to <16 yrs	Upper	31			
16 to <18 yrs	Upper	31			
18 to <21 yrs	Upper	31			
21+ yrs	Upper	44			
Lactating Woman	Upper	47			
Breastmilk Ingestion Rates, mL/kg-d (EPA Exposure Factors Handbook, 2011)					
Birth to <1 mon	Upper	220			
1 to <3 mons	Upper	190			
3 to <6 mons	Upper	150			
6 to <12 mons	Upper	130			

[a] Bartell et al., 2010; [b] Li et al., 2018; [c] Zhang et al., 2013; [d] MDH, 2018, 2019ab
[e] MIDHHS, 2019; [f] Thompson et al., 2010; [g] Sundström et al., 2012; Ali et al., *in review*
[h] ATSDR, 2018b;
[i] Body weight and age-specific adjustments to the V_d were maintained the same as described in Goeden et al., 2019.

Placental & breastmilk transfer ratios

NHDES applied previously selected placental and breastmilk transfer ratios for PFOA (MDH 2018), PFOS (MDH 2019), PFNA (MIDHHS 2019) and PFHxS (MDH 2019). In line with the MDH and MIDHHS, NHDES opted to use central tendency values for each PFAS versus the upper or 95th percentile estimate for transfer in the RME scenarios (Table 3).

The exact quantitative nature of PFAS transfer across the placenta remains an active area of research. For example, Mamsen et al. (2019) demonstrated that the accumulation of PFAS in fetal tissues begins early in pregnancy and continues throughout gestation as specific PFAS are taken up by the forming organs with slightly different efficiencies. Several studies of cord blood compared to maternal serum levels of PFAS have been used to estimate placental transfer ratios and are used in the model to predict the "at birth" serum level (Fei et al., 2007; Midasch et al., 2007; Monroy et al., 2008; Fromme et al., 2010; Beesoon et al., 2011; Kim et al., 2011; Liu et al., 2011; Needham et al., 2011; Lee et al., 2013; Porpora et al., 2013; Kato et al., 2014; Cariou et al., 2015; Manzano-Salgado et al., 2015; Fisher et al., 2016; Yang et al., 2016; Chen et al., 2017; Mamsen et al., 2019). The average maternal-to-cord blood or placenta ratios ranged from 0.20 (Mamsen et al., 2019) to 1.24 (Midasch et al., 2007) for PFOA, 0.14 (Fisher et al., 2014) to 0.60 (Midasch et al., 2007) for PFOS, 0.24 (Mamsen et al., 2019) to 1.18 (Monroy et al., 2008) for PFNA, and 0.23 (Fisher et al., 2016) to 1.25 (Monroy et al., 2008) for PFHxS. A point of caution in interpreting placental transfer ratios in these studies is the trimester of pregnancy that data are collected. Changes in blood volume over the coruse of pregnancy are expected to affect the maternal blood concentration, thereby influences cord blood to maternal blood concentration ratios for various PFAS. Collectively, these studies provide valuable and reliable information for estimating the transfer from mother to newborn. This model does not predict fetal blood or tissue concentrations of PFAS as this compartmentalization is poorly understood, although recent work, such as Mamsen et al. (2019) may lead to the development of such models.

Compared to placental transfer efficiencies that are well-documented for PFAS, a small body of literature informs our understanding of the PFAS in breastmilk. As a part of its review of the technical documents described by MDH (2018, 2019ab) and MIDHHS (2019), NHDES reviewed the source papers for the breastmilk transfer ratios (Karrman et al., 2007; Haug et al., 2011; Kim et al., 2011; Liu et al., 2011; Cariou et al., 2015; Gyllenhammer et al., 2018). These studies demonstrate that the small average percentage (0.6-11% across various PFAS) transferred from a mother's serum, which is typically at concentrations of ng/mL or ppb, results in breastmilk at concentration ranges well above most existing drinking water advisories. Combined with relatively high ingestion rates of breastmilk relative to the infant's body weight, this results in a spike of infant blood concentrations that the model predicts will remain high through childhood.

Duration of breastfeeding

A major assumption for the breastfeeding component of this model is the duration of exclusive breastfeeding. Consistent with the RME scenarios selected by other states (MDH, 2018, 2019ab; MIDHHS, 2019), NHDES used a 12-month duration of *exclusive breastfeeding* for all four RME scenarios. Similar to the CDC, the World Health Organization (WHO) defines exclusive breastfeeding as:

> "Exclusive breastfeeding means that the infant receives only breast milk. No other liquids or solids are given – not even water – with the exception of oral rehydration solution, or drops/syrups of vitamins, minerals or medicines." – WHO eLENA (2019)

A central tendency assumption for the duration of exclusive breastfeeding would be 6 months, but NHDES selected a more conservative modeling parameter of 12 months of exclusive breastfeeding. A 12-month exclusive breastfeeding duration is a conservative assumption because the CDC recommends 6 months of exclusive breastfeeding and some continuation through infancy given the clear benefits to an infant's health and their long-term development. After 6 months of age, the recommendation is that other food items are introduced and breastfeeding continues for up to 2 years of age.

This assumption has been argued by some to be overly conservative relative to the RME scenarios as 1) CDC recommended exclusive breastfeeding for up to 6 months of age and 2) if an infant were exclusively breastfeeding at or after 12 months of age, it is unlikely they are not ingesting other fluids or foods. NHDES contends that this is a reasonable assumption given 1) the role that the duration of exclusive breastfeeding plays in the MN model and 2) the high rates of breastfeeding in New Hampshire and breastfeeding trends across the nation.

MDH notes that the duration of breastfeeding, along with breastmilk intake rates and water concentration, are the most sensitive parameters of the model (MDH 2017). The duration of exclusive breastfeeding and breastfeeding with complimentary foods varies, but the CDC recommends up to 2 years of breastfeeding with the addition of complimentary foods. The transgenerational model does not contain parameters for apportionment of exposure from breastmilk versus complimentary foods, or formula, across the first two years of life. Given this uncertainty for mixed exposures for breastfed infants, NHDES agreed that the assumption of a 12-month exclusive breastfeeding duration was appropriate for estimate for the purpose of the model.

Results from the National Immunization Survey (NIS) indicate that, in the general U.S. population of newborns, approximately 24.9% ± 1.2 (± half 95% CI) of infants are exclusively breastfed at 6 months of age. By 12 months, 35.9% ± 1.3 of infants consume breastmilk along with complimentary foods and liquids (CDC, 2018a). New Hampshire specific estimates from this same dataset are that 30.2% ± 5.8 of infants exclusively breastfeed at 6 months of age, while 45.6% ± 6.5 breastfeed at 12 months of age in addition to complimentary foods (CDC, 2018a). Based on the historical trends, the 2018 Breastfeeding Report Card (CDC, 2018b) indicates more women nationwide are breastfeeding or want to breastfeed their children, giving weight to the consideration of breastfeeding and selecting a conservative window of 12 months.

Breastmilk and drinking water ingestion rate assumptions

This transgenerational model evaluates the impact of changing water ingestion rates across a lifespan. These ingestion rates are expressed as liters of water per kilogram of an individual's body weight per day (L/kg-d). As a person grows, their physiological demand for water changes and this is reflected by age-specific ingestion rates, or life-process specific rates in the case of pregnant and lactating women. To put this in context of historical practice, the EPA typically assumed a drinking water ingestion rate of 2 L/d

for adults and 1 L/d for infants and children under 10 years of age (U.S. EPA, 2000). After adjusting for body weight, these typical rates would underestimate the water consumption of infants, children and lactating and pregnant women. Thus, consideration of these life-stage specific values is prudent for a persistent and highly-bioaccumulative class of drinking water contaminants.

To be protective of the general population including high-end water consumers, NHDES applied the 95th percentile water and breastmilk ingestion rates throughout life in the RME scenarios for PFOA, PFOS, PFHxS and PFNA. The use of the 95th percentile for water ingestion rates is consistent with the initial proposal, and this is simply an extension to other life stages. Recently updated values in 2019 Updated Chapter 3 of the Exposure Factors Handbook (EPA, 2019) were combined with estimated breastmilk ingestion rates from Chapter 15 of the 2011 Edition (EPA, 2011). As these changes were specific to water ingestion, not breastmilk, the difference between the 2011 and 2019 estimates for infants, a change of -9% to +3% for those <1 year of age, was determined to be a minor and tolerable change to the RME scenarios. The breastfed RME exposure was the driver of the MCL for all evaluated PFAS, and therefore protective of an individual in the formula-fed RME scenario.

Consideration of the Relative Source Contribution (RSC)

Exposure to PFAS is not solely due to drinking water, so in order for the MCL to be health protective NHDES needs to account for the contribution of other sources towards the reference dose (RfD). The proportion of exposure attributed to a specific source is accounted for through the relative source contribution (RSC). With respect to a MCL, the RSC is the percentage of total exposure typically accounted for by drinking water (EPA 2000). This value can be referred to as a proportion or percentage, and EPA recommends a ceiling of 80% and a floor of 20%. A smaller RSC for drinking water exposure results in a lower regulatory standard, but implies that sources other than water contribute more significantly to exposure.

Presently, there is no inventory of all relevant sources of PFAS exposure to determine what proportion each source shares in an RSC for the general population. Several studies have characterized specific media such as dust, food (Kowalczyk et al., 2013; reviewed by EFSA, 2018) and breastmilk (previously discussed) and estimated the percentages of total exposure attributable to these sources; but no single study has merged these findings to estimate the reasonable and realistic RSC for drinking water.

In the absence of such data, the EPA provides a decision tree for identifying an appropriate RSC (replicated in Figure 1; EPA 2000). Following this process, NHDES determined:

- (Box 6 to 8a) *Yes, there are significant known sources of these PFAS other than drinking water*. As a result of their dispersion into the environment and lack of adequate removal from waste streams, there are known sources of PFAS that contribute to environmental exposures. This includes release into surface water and implications for fish and shellfish consumption (Fair et al., 2019), and the impacts of PFAS contamination of soil (Filipovic et al., 2015; Scher et al., 2018), dust (Fu et al., 2015; Winkens et al., 2018) and agriculture-related exposures (Nascimento et al., 2018; reviewed by Ghisi et al., 2019).

- (Box 8a to 8c) *Yes, there is some information to make a characterization of exposure*. As mentioned above, there is some data on environmental sources to make rough characterizations. Additionally, there is blood data from the National Health and Nutrition Examination Survey (NHANES) to estimate the general exposure of the U.S. population to PFAS. The NHANES data for blood levels of PFAS is assumed to reflect general exposure to all sources in the U.S. population, and is presumed to not reflect the results of excessively high exposures, relative to the proposed MCLs, due to contaminated drinking water as seen in the communities of Southern New Hampshire Pease Tradeport and Southern New Hampshire.
- (Box 8c to 13) *NHDES performed apportionment with a 50% ceiling and 20% floor for each of the assessed PFAS*. This apportionment was achieved using the EPA subtraction method (EPA 2000).

The subtraction method (EPA 2000) estimates an apportionment of the RSC is based on assumed knowledge of the background exposure. For PFAS, the subtraction method has been mathematically applied as follows (NJDWQI 2018; MDH 2018, 2019ab):

$$\text{Relative Source Contribution} = \frac{\text{Target serum level } \left(\frac{\text{ng}}{\text{mL}}\right) - \text{Reference or background population level } \left(\frac{\text{ng}}{\text{mL}}\right)}{\text{Target serum level } \left(\frac{\text{ng}}{\text{mL}}\right)} \times 100\%$$

The difference between the target serum level and the RfD is that the former is an internal blood concentration while the latter is the external amount of the chemical that could come from multiple sources. For each of the compounds, the target serum levels were: PFOA – 43.5 ng/mL, PFOS – 23.6 ng/mL, PFNA – 49.0 ng/mL and PFHxS – 46.3 ng/mL. The reference population serum level is meant to reflect a background level of exposure from the general population, not one that is highly exposed due to a specific environmental source such as drinking water. Using the NHANES average serum values, subtracting this background level from the target serum level (the maximum allowable level) results in a proportion that is presumably permissible for drinking water alone. Other sources including food, dust, treated consumer products (e.g., carpeting, cookware, food packaging, etc.) are assumed to be included in the reference or background population blood concentrations.

Using this approach with the NHANES 2013-2014 data for children ranging in age from 3 to 19 years (as reported in Daly et al., 2018), NHDES arrived at RSCs of 50% for PFOA, PFOS, PFNA and PFHxS. Unlike its initial proposal, NHDES selected the NHANES dataset over the use of NH-specific estimates. The NH-specific blood data was focused on communities whose primary exposure was associated with drinking water, and would therefore overestimate non-drinking water exposure sources if used to establish an RSC as initially proposed in January (NHDES, 2019). Thus, the NHANES dataset was deemed more appropriate to account for other non-drinking water sources of exposure. For an understanding of how the NHANES data compares to that collected from one of the highly-exposed communities in New Hampshire and the limitations of interpreting these findings, readers are referred to Daly et al. (2018).

Instead of using the general population (i.e., all ages), NHDES estimated RSCs based on the serum concentrations from those younger than 19 years of age (Table 4). As emphasized in several comments made to NHDES on its initial proposal, the risk assessment needs to consider current information for children. Since the phase out of certain PFAS, but not all, the national average serum levels have declined suggesting some reduction of background exposure. Given the emphasis of the RME on infancy

and early childhood, NHDES determined it was appropriate to derive the RSC with specific consideration of this group. All of the values for PFOA, PFOS, PFNA and PFHxS were at or above 48.3%, therefore NHDES opted for an RSC of 50%.

NHDES acknowledges that the use of the general NHANES estimates that includes adults with historically high exposures results in similar or more restrictive RSC values; especially for PFOS. However, the RME scenarios for the proposed MCLs indicate that the predicted serum level for the 95th percentile of adult water consumers is approximately equal to or below the 20% RSC and therefore sufficiently protective after considering the context of the national dataset. Furthermore, the cap of 50% despite calculated higher RSCs for each of these accounts for the unknown and novel sources of PFAS exposure, as well as the higher serum levels of PFAS found in New Hampshire's highly-exposed communities.

Table 4. Relative Source Contribution Estimates. Various relative source contribution (RSC) values resulting from use of the EPA subtraction method (EPA 2002) in combination with available serum data for the geometric mean (GM) and 95th percentile from the NHANES 2013-2014 dataset, as reported in Daly et al. (2018).

Reference Population	Reference Serum level (ng/mL)	Target Serum Level (ng/mL)	Resulting RSC Allotment for Drinking Water (%)
PFOA			
3-5 year olds (GM)	2.00	43.5	95.4
6-11 year olds (GM)	1.89	43.5	95.7
12-19 year olds (GM)	1.66	43.5	96.2
3-5 year olds (95th percentile)	5.58	43.5	87.2
6-11 year olds (95th percentile)	3.84	43.5	91.2
12-19 year olds (95th percentile)	3.47	43.5	92.0
PFOS			
3-5 year olds (GM)	3.38	24.0	85.9
6-11 year olds (GM)	4.15	24.0	82.7
12-19 year olds (GM)	3.54	24.0	85.3
3-5 year olds (95th percentile)	8.82	24.0	63.3
6-11 year olds (95th percentile)	12.40	24.0	48.3
12-19 year olds (95th percentile)	9.30	24.0	61.3
PFNA			
3-5 year olds (GM)	0.76	49.0	98.4
6-11 year olds (GM)	0.81	49.0	98.3
12-19 year olds (GM)	0.60	49.0	98.8
3-5 year olds (95th percentile)	3.49	49.0	92.9
6-11 year olds (95th percentile)	3.19	49.0	93.5
12-19 year olds (95th percentile)	2.00	49.0	95.9
PFHxS			
3-5 year olds (GM)	0.72	46.3	98.4
6-11 year olds (GM)	0.91	46.3	98.0
12-19 year olds (GM)	1.27	46.3	97.3
3-5 year olds (95th percentile)	1.62	46.3	96.5
6-11 year olds (95th percentile)	4.14	46.3	91.1
12-19 year olds (95th percentile)	6.30	46.3	86.4

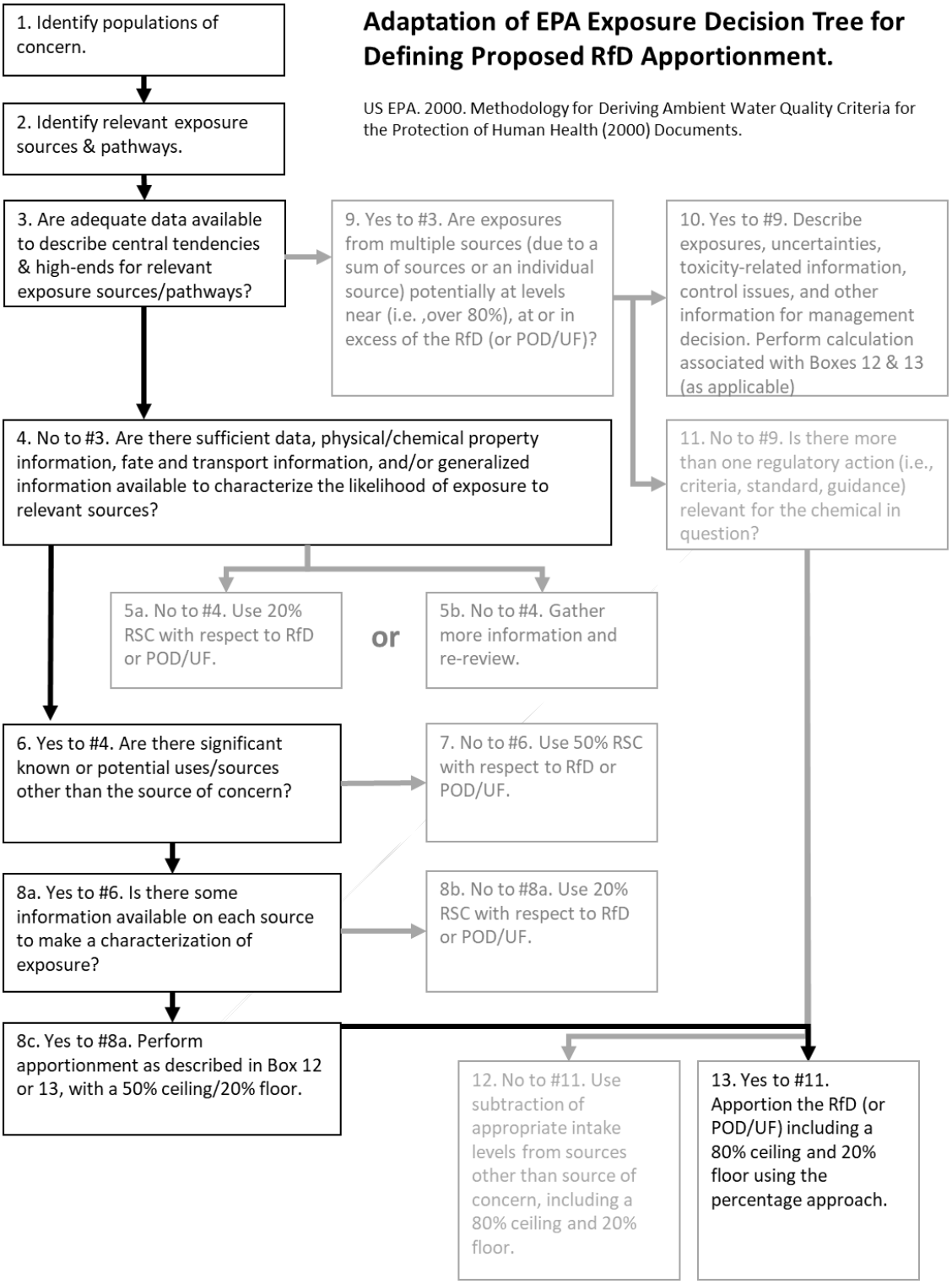

Figure 1. Adaptation of EPA decision tree (EPA, 2000) for determining the RSC. Black boxes, text and arrows outline the decision process used by NHDES to arrive at the subtraction method for PFAS with a 50% ceiling. The target serum level is a population assessment value, *not clinical*, from the derivation of the RfDs, detailed in Section III.

Section V. Discussion of the MCLs proposed by NHDES

Based on the previously described RfDs, exposure considerations and application of the transgenerational model (Figure 2), the proposed maximum contaminant levels (MCLs) are:

- **12 ng/L for Perfluorooctanoic acid, or perfluorooctanoate (PFOA)**
- **15 ng/L for Perfluorooctane sulfonic acid, or perfluorooctane sulfonate (PFOS)**
- **11 ng/L for Perfluorononanoic acid, or perfluorononanoate (PFNA)**
- **18 ng/L for Perfluorohexane sulfonic acid, or perfluorohexane sulfonate (PFHxS)**

These health-based values are intended as health-protective limits against the chronic health effects for a through-life exposure. The primary associated health outcomes are hepatotoxicity and changes in lipid metabolism (PFOA and PFNA), suppressed immune response to vaccines (PFOS) and impaired female fertility (PFHxS). Secondary associated health effects that are expected to be less sensitive are changes in thyroid and sex hormone levels, early-life growth delays, changes in cholesterol levels and biomarkers of liver function, neurobehavioral effects, and a possible risk for certain cancers (i.e., testicular and kidney).

Modeled Exposure Results

Figure 2 shows the model result for predicted serum concentrations at the proposed MCL for each PFAS. The exposure starts at birth with the assumption that the mother is at a steady-state serum level from consumption of water at the modeled drinking water concentration. The solid blue line represents the highest exposure in the RME model, showing the predicted serum level for a breastfed infant who consumes breastmilk and water at the 95th percentile ingestion rates throughout life and is born to and breastfeeds from a mother with a similar water consumption rate. The solid green line represents the predicted serum level for a formula-fed infant who consumes formula (reconstituted with water at the MCL) and water at the 95th percentile ingestion rates throughout life and is born to a mother with a similar water consumption rate. The dashed lines represent the predicted serum concentrations for individuals at the central tendency or average breastmilk, formula and water ingestion rates.

There is a clear spike in predicted serum levels of breastfed infants due to the aforementioned transfer efficiencies of PFAS into breastmilk. For infants, this is concerning due to the potential for hand-to-mouth behaviors in later infancy that have been shown to contribute to PFAS exposure in children of this age (Trudel et al., 2008). Because of these potential exposures and the suspected health impacts on early development, NHDES selected an MCL value that does not allow the predicted infant serum level to exceed the 50% RSC of the RfD or target serum level. It is true that the central tendency consumers fall well below this threshold. However, it has been shown that when considering variants on the RME scenarios the use of the 95th percentile ingestion rate is adequately protective for other factors (e.g., higher breastmilk transfer efficiencies or longer half-life estimates) (Goeden et al., 2019).

The long half-lives of these compounds result in significantly elevated serum levels peaking at the cessation of breastfeeding and continuing through the remainder of childhood. While the predicted steady-state concentrations for adults or formula-fed infants would allow less restrictive MCLs, breastfed children could potentially exceed the RfD due to other sources such as dust (Winkens et al., 2018) or foods and food packaging (D'eon et al., 2009; reviewed by EFSA, 2018). This point further emphasizes the appropriateness of the 50% cap on the RSC as selected by NHDES.

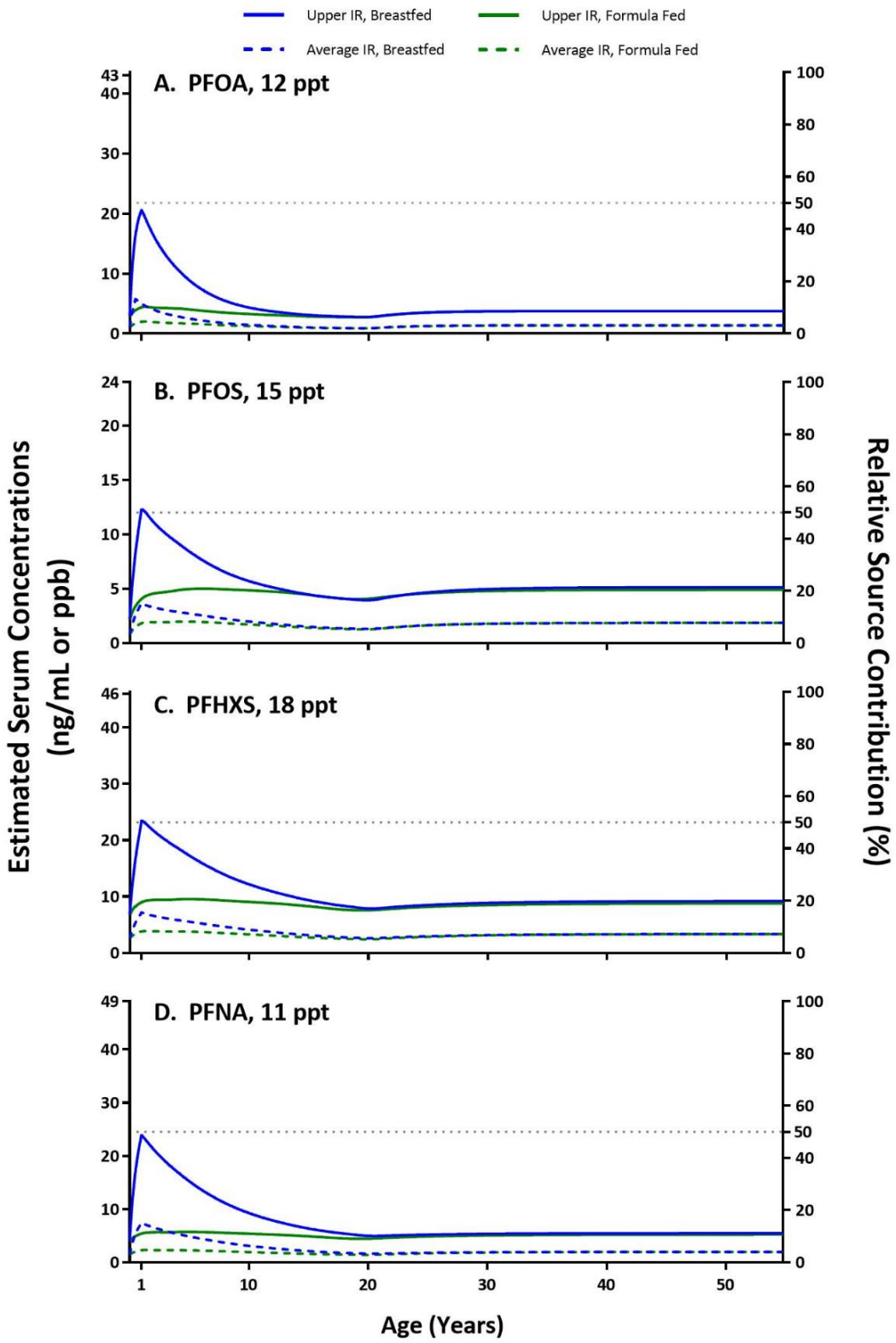

Figure 2. Predicted serum PFAS concentrations in response to upper (95th percentile) and average (mean) water ingestion rates (IR) at the proposed MCLs. Blue lines indicate results for breastfed infants with 12 months exclusive breastfeeding, and green lines indicate results for formula-fed infants. Solid lines represent upper IRs and dashed lines indicate average (mean) IRs. Estimates made using the model described in Goeden et al. (2019).

Using the proposed MCL values for each compound, serum concentrations attributable to drinking water can be estimated for an individual across various life stages (adapted from Figure 2). For newborns (at birth), the estimated drinking water contribution to serum concentrations for the 95th percentile consumer would be: 2.9 ng/mL for PFOA, 2.2 ng/mL for PFOS, 4.0 ng/mL for PFNA and 6.9 ng/mL for PFHxS. The model does not predict fetal tissue concentrations, so the predicted at-birth values represent the aforementioned placental transfer efficiencies. The predicted drinking water contribution to serum concentrations for the 95th percentile breastmilk consumer (at the end of 1 year of exclusive breastfeeding) would be: 20.6 ng/mL for PFOA, 12.4 ng/mL for PFOS, 25.1 ng/mL for PFNA and 23.5 ng/mL for PFHxS. Adults at steady state following constant water consumption at the 95th percentile are predicted to have drinking water contributions of PFAS equal to or less than: 3.8 ng/mL for PFOA, 5.1 ng/mL for PFOS, 5.7 ng/mL for PFNA and 9.2 ng/mL for PFHxS.

As a point of caution in interpretation, the previously described results assume no fluctuation from the 95th percentile drinking water consumption rate across an individual lifespan. That is to say, the 95th percentile consumer remains the 95th percentile consumer every day. These estimates include several conservative and protective assumptions, such as the use of the 95th percentile of drinking water ingestion rates (adjusted for body weight) throughout life, not the average water consumer or fluctuations between these tendencies. Additionally, the modeled outputs may not reflect individual variations in biology throughout life (Fàbrega et al., 2014; Worley et al., 2017) and are intended for population-level exposure assessment. However, as described by Goeden et al. (2019), this fit-for-purpose tool provides important insight into exposures during critical life stages of development. Further development and refinement of multi-compartment models will certainly prove useful for future risk assessments of these and other PFAS.

The proposed MCLs are predicted to result in a modest increase of serum concentrations due to drinking water levels; but, as argued by Post et al. (2017), such increases relative to background are preferred over the significantly larger serum levels that are predicted for the previously proposed MCLs (NHDES, 2019) or the EPA lifetime health advisories (EPA, 2016ab). Based on current evidence, this level of exposure is expected to be sufficiently health protective relative to current background levels reported in populations of concern, such as children and adolescents (Table 4).

Limitations and uncertainties

As with any risk assessment, this process was subject to uncertainty and limitations. Limitations included recommendation of individual versus group-based MCLs for PFAS, and consideration of background exposure using the RME scenarios described in Section IV. A major uncertainty was quantifying the exact risks of disease incidence for each compound, which is also a significant challenge for quantifying, or monetizing, the benefits of the proposed MCLs.

A limitation to the present assessment is that the transgenerational model's RME scenarios focus on the predicted impact of drinking water exposure, not other background sources of exposure. In general, there is a downward trend for the background levels of most measured PFAS based on the NHANES data. NHDES considered this with its use of the NHANES data to derive and apply a 50% RSC for each compound. Although PFOA and PFOS were recently phased out by most U.S. manufacturers, there remains potential for exposure to these and other PFAS from imported products or the degradation of

precursors into PFOA or PFOS in the environment. Nevertheless, the appropriate level of conservatism applied in the assumptions of drinking water ingestion rates and RSC provide reasonable protection.

At this time, NHDES is not recommending a class-based approach to regulation of these compounds. This is a limitation of the present risk assessment given the considerable number of PFAS detected in the environment and used in commerce. However, individual assessment of each compound found each one to have relatively unique toxico-dynamic and –kinetic properties based on consideration of existing animal toxicity and human data. Despite similarity in the range of the proposed MCLs for these 4 PFAS, it is likely that future individual assessments, using current EPA methodology, of shorter carbon chain PFAS will result in higher drinking water values for shorter carbon chain compounds as a result of shorter half-lives. Given these considerations, it was determined that a class based approach was not advisable at this time. Should other state agencies or the U.S. EPA identify science-based methods for group regulation that account for some of the unique properties of these compounds, NHDES will consider this approach.

Currently, there is uncertainty to quantifying the health risks associated with exposure to PFOA, PFOS, PFNA, PFHxS and other PFAS. A growing number of epidemiological and animal toxicity studies are adding to the body of evidence for the biological activity and health outcomes associated with these contaminants. However, the exact nature of PFAS-related health hazards remains elusive due to a variety of factors including, but not limited to: a limited understanding of the toxicological mechanism of action, their occurrence world-wide and lack of control (i.e., PFAS-free) populations to compare health outcomes against, lack of long-term studies despite decades of use, and co-exposure with other PFAS and other environmental contaminants. Additional research is critically needed to address this issue and better characterize and quantify the risks associated with PFAS.

Conclusions

The lower MCLs proposed in this report are primarily due to consideration of the elevated serum levels predicted for infants and young children under a reasonable maximum exposure scenario. At the initially proposed values, these spikes in infant blood levels of PFAS would result in unacceptable reductions in the margin of exposure from infancy through childhood due to the unique properties of PFAS. Their capacity to transfer through breastmilk combined with relatively long half-lives of each compound merits the use of novel methods (i.e., Goeden et al., 2019) to provide a more accurate assessment of exposure. This is not a recommendation against breastfeeding for women who are currently breastfeeding or plan to breastfeed as the benefits of breastfeeding are very well-defined relative to the potential risk associated with PFAS. NHDES recommends these MCLs to afford adequate long-term health protection of the population based on its assessment of these four PFAS.

The human health impacts of PFAS is a continuously evolving area of scientific research, and is expected to continue changing in the future. The assessments made by NHDES are based on currently available information but recognizes that science is a process, not an outcome. Future assessments of these and other PFAS compounds may result in higher or lower health protective values based on the best available science at the time. NHDES will continue to review emerging information as a part of its ongoing efforts to understand the impacts of PFAS contamination across New Hampshire.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2018a. Toxic Substances Portal: Minimal Risk Levels (MRLs) – For Professionals. Updated June 21, 2018. https://www.atsdr.cdc.gov/mrls/index.asp

Agency for Toxic Substances and Disease Registry (ATSDR). 2018b. Toxicological Profile for Perfluoroalkyls – Draft for Public Comment, June 2018. Accessed online at: https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf.

Albrecht PP, Torsell NE, Krishnan P, et al. 2013. A species difference in the peroxisome proliferator-activated receptor α-dependent response to the developmental effects of perfluorooctanoic acid. Toxicol Sci 131(2):568-582.

Ali JM, Roberts SM, Gordon DS, Stuchal LD. (in review) Derivation of a chronic reference dose for perfluorohexane sulfonate (PFHxS) for reproductive toxicity in mice.

Ballesteros V, Costa O, Iñiguez C, Fletcher T, Ballester F, Lopez-Espinosa MJ. 2017. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. Environ Int, 99:15-28. doi: 10.1016/j.envint.2016.10.015.

Bartell SM, Calafat AM, Lyu C, et al. 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118(2):222-228

Barry V, Winquist A, Steenland K. 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect 121(11-12):1313-1318.

Bassler J, Ducatman A, Elliott M, Wen S, Wahlang B, Barnett J, Cave MC. 2019. Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. Environ Pollut. 247:1055-1063. doi: 10.1016/j.envpol.2019.01.064

Beesoon S, Webster GM, Shoeib M, Harner T, Benskin JP, Martin JW. 2011. Isomer profiles of perfluorochemicals in matched maternal, cord, and house dust samples: manufacturing sources and transplacental transfer. Environ Health Perspect. 119(11):1659-64. doi: 10.1289/ehp.1003265.

Bijland S, Rensen PC, Pieterman EJ, et al. 2011. Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. Toxicol Sci 123(1):290-303. 10.1093/toxsci/kfr142.

Boronow KE, et al. 2019. Serum concentrations of PFASs and exposure-related behaviors in African American and non-Hispanic white women. Journal of Exposure Science & Environmental Epidemiology, pp. 1-12.

Butenhoff J, Costa G, Elcombe C, et al. 2002. Toxicity of ammonium perfluorooctanoate in male Cynomolgus monkeys after oral dosing for 6 months. Toxicol Sci 69(1):244-257.

Butenhoff JL, Chang S, Ehresman DJ, et al. 2009a. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reprod Toxicol 27:331-341.

Butenhoff JL, Ehresman DJ, Chang SC, et al. 2009b. Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: Developmental neurotoxicity. Reprod Toxicol 27(3-4):319-330.

Butenhoff JL, et al. 2008. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reproductive Toxicology, 27, 331-341.

Butenhoff, J.L., G.L. Kennedy, Jr., S.-C. Chang, and G.W. Olsen. 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology 298:1–13.

Butenhoff, J.L., G.L. Kennedy, S.R. Frame, J.C. O'Conner, and R.G. York. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. Toxicology 196:95–116.

California Office of Environmental Health Hazard Assessment. 2019. PFOA and PFOS Notification Levels. https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/PFOA_PFOS.html

Cariou R, Veyrand B, Yamada A, et al. 2015. Perfluoroalkyl acid (PFAA) levels and profiles in breast milk, maternal and cord serum of French women and their newborns. Environ Int 84:71-81.

Chang ET, et al. 2016. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Crit Rev Toxicol., 46(4): 279-331.

Chang S, et al. 2018. Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. Reproductive Toxicology 78: 150-168.

Chen F, Yin S, Kelly BC, Liu W. 2017. Isomer-Specific Transplacental Transfer of Perfluoroalkyl Acids: Results from a Survey of Paired Maternal, Cord Sera, and Placentas. Environ Sci Technol. 51(10):5756-5763. doi: 10.1021/acs.est.7b00268.

Cheng J, Fujimura M, Zhao W, et al. 2013. Neurobehavioral effects, c-Fos/Jun expression and tissue distribution in rat offspring prenatally co-exposed to MeHg and PFOA: PFOA impairs Hg retention. Chemosphere 91(6):758-764.

Cui L, Zhou QF, Liao CY, et al. 2009. Studies on the toxicological effects of PFOA and PFOS on rats using histological observation and chemical analysis. Arch Environ Contam Toxicol 56(2):338-349.

Cui Y, et al. 2015. Investigation of the Effects of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) on Apoptosis and Cell Cycle in a Zebrafish (Danio rerio) Liver Cell Line. Int J Environ Res Public Health. 12(12):15673-82.

Daly ER, Chan BP, Talbot EA, Nassif J, Bean C, Cavallo SJ, Metcalf E, Simone K, Woolf AD. 2018. Per- and polyfluoroalkyl substance (PFAS) exposure assessment in a community exposed to contaminated drinking water, New Hampshire, 2015. Int J Hyg Environ Health. 221(3):569-577. doi: 10.1016/j.ijheh.2018.02.007.

Das KP, Grey BE, Rosen MB, et al. 2015. Developmental toxicity of perfluorononanoic acid in mice. Reprod Toxicol 51:133-144. 10.1016/j.reprotox.2014.12.012.

Das KP, Wood CR, Lin MT, et al. 2017. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. Toxicology 378:37-52. 10.1016/j.tox.2016.12.007.

D'eon JC, Crozier PW, Furdui VI, Reiner EJ, Libelo EL, Mabury SA. 2009. Observation of a commercial fluorinated material, the polyfluoroalkyl phosphoric acid diesters, in human sera, wastewater treatment plant sludge, and paper fibers. Environ. Sci. Technol. 43: 4589-4594.

DeWitt JC, Blossom SJ, Schaider LA. 2019. Exposure to per-fluoroalkyl and polyfluoroalkyl substances leads to immunotoxicity: epidemiological and toxicological evidence. J Expo Sci Environ Epidemiol. 29(2):148-156. doi: 10.1038/s41370-018-0097-y

DeWitt JC, Peden-Adams MM, Keller JM, Germolec DR. 2012. Immunotoxicity of Perfluorinated Compounds: Recent Developments. Toxicologic Pathology, 40: 300-311.

Dong GH, Liu MM, Wang D, et al. 2011. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. Arch Toxicol 85(10):1235-1244.

Dong GH, Zhang YH, Zheng L, et al. 2009. Chronic effects of perfluorooctanesulfonate exposure on immunotoxicity in adult male C57BL/6 mice. Arch Toxicol 83(9):805-815.

Elcombe CR, Elcombe BM, Foster JR, et al. 2010. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPARα and CAR/PXR. Arch Toxicol 84(10):787-798.

Ernst A, Brix N, Lauridsen LLB, Olsen J, Parner ET, Liew Z, Olsen LH, Ramlau-Hansen CH. 2019. Exposure to Perfluoroalkyl Substances during Fetal Life and Pubertal Development in Boys and Girls from the Danish National Birth Cohort. Environ Health Perspect. 127(1):17004. doi: 10.1289/EHP3567.

European Food Safety Authority (EFSA). 2018. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA Journal, 16(12):5194

Fàbrega F, Kumar V, Schuhmacher M, Domingo JL, Nadal M. 2014. PBPK modeling for PFOS and PFOA: validation with human experimental data. Toxicol Lett. 230(2):244-51. doi: 10.1016/j.toxlet.2014.01.007.

Fair PA, Wolf B, White ND, Arnott SA, Kannan K, Karthikraj R, Vena JE. 2019. Perfluoroalkyl substances (PFASs) in edible fish species from Charleston Harbor and tributaries, South Carolina, United States: Exposure and risk assessment. Environ Res. 171:266-277. doi: 10.1016/j.envres.2019.01.021

Fang X, Fenga Y, Wang J, et al. 2010. Perfluorononanoic acid-induced apoptosis in rat spleen involves oxidative stress and the activation of caspase-independent death pathway. Toxicology 267: 54-59

Fei C, McLaughlin JK, Tarone RE, et al. 2007. Perfluorinated chemicals and fetal growth: A study within the Danish National Birth Cohort. Environ Health Perspect 115:1677-1682.

Filipovic M., Woldegiorgis A., Norström K., Bibi M., Lindberg M., Österås A.H. Historical usage of aqueous film forming foam: A case study of the widespread distribution of perfluoroalkyl acids from a military airport to groundwater, lakes, soils and fish. Chemosphere. 2015;129:39–45. doi: 10.1016/j.chemosphere.2014.09.005

Fisher M, Arbuckle TE, Liang CL, et al. 2016. Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ Health 15(1):59.

Fromme H, Mosch C, Morovitz M, et al. 2010. Pre- and postnatal exposure to perfluorinated compounds (PFCs). Environ Sci Technol 44(18):7123-7129.

Fu J, Gao Y, Wang T, Liang Y, Zhang A, Wang Y, Jiang G. 2015. Elevated levels of perfluoroalkyl acids in family members of occupationally exposed workers: the importance of dust transfer. Sci Rep. 20;5:9313. doi: 10.1038/srep09313.

Ghisi R, Vamerali T, Manzetti S. 2019. Accumulation of perfluorinated alkyl substances (PFAS) in agricultural plants: A review. Environ Res. 169:326-341. doi: 10.1016/j.envres.2018.10.023.

Gleason JA, Post GB, Fagliano JA. 2015. Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007-2010. Environ Res 136:8-14. 10.1016/j.envres.2014.10.004.

Goeden HM, Greene CW, Jacobus JA. 2019. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. J Expo Sci Environ Epidemiol. 29(2):183-195. doi: 10.1038/s41370-018-0110-5.

Grandjean P, et al. 2012. Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds. JAMA, 307(4): 391-397.

Grandjean P, Landrigan PJ. (2014). Neurobehavioural effects of developmental toxicity. Lancet Neurol . 13, 330–338.

Gyllenhammar I, Benskin JP, Sandblom O, Berger U, Ahrens L, Lignell S, Wiberg K, Glynn A. 2018. Perfluoroalkyl Acids (PFAAs) in Serum from 2-4-Month-Old Infants: Influence of Maternal Serum Concentration, Gestational Age, Breast-Feeding, and Contaminated Drinking Water. Environmental Science and Technology. 2018 Jun 19;52(12):7101-7110. doi: 10.1021/acs.est.8b00770

Hagenaars A, et al. 2013. Mechanistic toxicity study of perfluorooctanoic acid in zebrafish suggests mitochondrial dysfunction to play a key role in PFOA toxicity. Chemosphere, 91(6): 844-56.

Hall AP, Elcombe CR, Foster JR, et al. 2012. Liver hypertrophy: A review of adaptive (adverse and non-adverse) changes- conclusions from the 3rd International ESTP Expert Workshop. Toxicol Pathol 40:971-994.

Haug LS, et al. 2011. Investigation on Per- and Polyfluorinated Compounds in Paired Samples of House Dust and Indoor Air from Norwegian Homes. Environmental Science & Technology, 45, 7991-7998.

Haug LS. 2011. Characterisation of human exposure pathways to perfluorinated compounds – comparing exposure estimates with biomarkers of exposure. Dissertation for the degree of Doctor of Philosophiae, University of Oslo.

Haug, L.S., Huber, S., Becher, G., Thomsen, C. 2011. Characterisation of human exposure pathways to perfluorinated compounds - comparing exposure estimates with biomarkers of exposure. Environ. Int. 37: 687-693.

Health Canada. 2016a. Perfluorooctanoic acid (PFOA) in drinking water. Available online at: https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/health-system-systeme-sante/consultations/acide-perfluorooctanoic-acid/alt/perfluorooctanoic-eng.pdf

Health Canada. 2016b. Perflurooctane sulfonate (PFOS) in drinking water. Available online at: https://www.canada.ca/content/dam/hc-sc/healthy-canadians/migration/health-system-systeme-sante/consultations/perfluorooctane-sulfonate/alt/perfluorooctane-sulfonate-eng.pdf

Hu Q, Strynar MJ, DeWitt JC. 2010. Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA? J Immunotoxicol 7(4):344-349.

International Agency for Research on Cancer (IARC) 2016: CAS No. 335-67-1, Agent = Perfluorooctanoic acid (PFOA) Group 2B, Volume 110, 2016 online, Available at: http://monographs.iarc.fr/ENG/Classification/latest_classif.php

Jain RB, Ducatman A. 2019. Selective Associations of Recent Low Concentrations of Perfluoroalkyl Substances with Liver Function Biomarkers: NHANES 2011 to 2014 Data on US Adults Aged ≥20 Years. J Occup Environ Med. 61(4):293-302.

Kang H, et al. 2016. Elevated levels of short carbon-chain PFCAs in breast milk among Korean women: Current status and potential challenges. Environmental Research, 148, 351-359.

Kärrman A, Ericson I, van Bavel B, et al. 2007. Exposure of perfluorinated chemicals through lactation: Levels of matched human milk and serum and a temporal trend, 1996-2004, in Sweden. Environ Health Perspect 115:226-230.

Kato K, Wong LY, Chen A, et al. 2014. Changes in serum concentrations of maternal poly- and perfluoroalkyl substances over the course of pregnancy and predictors of exposure in a multiethnic cohort of Cincinnati, Ohio pregnant women during 2003-2006. Environ Sci Technol 48(16):9600-9608.

Kim D-H, et al. 2019. Assessment of individual-based perfluoroalkyl substances exposure by multiple human exposure sources. Journal of Hazardous Materials, 365, 26-33.

Kim SK, Lee KT, Kang CS, et al. 2011. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. Environ Pollut 159(1):169-174.

Kirk M, Smurthwaite K, Bräunig J et al. (2018). The PFAS Health Study: Systematic Literature Review. Canberra: The Australian National University.

Klaunig JE, Hocevar BA, Kamendulis LM. 2012. Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance. Reprod Toxicol 33(4):410-418.

Koskela A, Finnila MA, Korkalainen M, et al. 2016. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicol Appl Pharmacol 301:14-21. 10.1016/j.taap.2016.04.002.

Koustas E, Lam J, Sutton P, et al. 2014. The Navigation Guide - evidence-based medicine meets environmental health: Systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect 122(10):1015-1027.

Kowalczyk J., Ehlers S., Oberhausen A., Tischer M., Furst P., Schafft H., Lahrssen-Wiederholt M. Absorption, distribution, and milk secretion of the perfluoroalkyl acids PFBS, PFHxS, PFOS, and PFOA by dairy cows fed naturally contaminated feed. J. Agric. Food Chem. 2013;61:2903–2912. doi: 10.1021/jf304680j

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol. Sci. 99: 366-394.

Lau C, Thibodeaux JR, Hanson RG, et al. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: Postnatal evaluation. Toxicol Sci 74(2):382-392.

Lau C, Thibodeaux JR, Hanson RG, et al. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci 90(2):510-518.

Lee SS-T, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H, and Gonzalez FJ. 1995. Targeted disruption of the a isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. Mol Cell Biol 15:3012–3022

Lee YJ, Kim M-K, Bae J, et al. 2013. Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in Korea. Chemosphere 90(5):1603-1609.

Li K, Gao P, Xiang P, Zhang X, Cui X, Ma LQ. 2017a. Molecular mechanisms of PFOA-induced toxicity in animals and humans: Implications for health risks. 99:43-54.

Li K, Sun J., Yang J, Roberts SM, Zhang X, Cui X, Wei S, Ma LQ. 2017b. Molecular Mechanisms of Perfluorooctanoate-Induced Hepatocyte Apoptosis in Mice Using Proteomic Techniques. Environmental Science & Technology, 51, 11380-11389.

Li Y, Fletcher T, Mucs D, et al. 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med 75(1):46-51. 10.1136/oemed-2017-104651.

Liew Z, et al. 2018. Developmental Exposures to Perfluoroalkyl Substances (PFASs): An Update of Associated Health Outcomes. Current Environmental Health Reports 5:1-19.

Liu J, Li J, Liu Y, et al. 2011. Comparison on gestation and lactation exposure of perfluorinated compounds for newborns. Environ Int 37(7):1206-1212.

Loveless SE, Finlay C, Everds NE, et al. 2006. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology 220:203-217.

Loveless SE, Hoban D, Sykes G, et al. 2008. Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. Toxicol Sci 105(1):86-96.

Luebker DJ, Case MT, York RG, et al. 2005a. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology 215(1-2):126-148.

Luebker DJ, York RG, Hansen KJ, et al. 2005b. Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: Dose-response, and biochemical and pharmacokinetic parameters. Toxicology 215(1-2):149-169.

Macon MB, Villanueva LR, Tatum-Gibbs K, et al. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: Low-dose developmental effects and internal dosimetry. Toxicol Sci 122(1):134-145.

Mamsen LS, Björvang RD, Mucs D, Vinnars MT, Papadogiannakis N, Lindh CH, Andersen CY, Damdimopoulou P. 2019. Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies. Environ Int. 124:482-492. doi: 10.1016/j.envint.2019.01.010. Epub 2019 Jan 24.

Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, et al. 2015. Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environ Res 142:471-478. 10.1016/j.envres.2015.07.020

Michigan Department of Health and Human Services (MIDHHS). 2019. Public health drinking water screening levels for PFAS. Available online at: https://www.michigan.gov/documents/pfasresponse/MDHHS_Public_Health_Drinking_Water_Screening_Levels_for_PFAS_651683_7.pdf

Michigan PFAS Science Advisory Panel Report. 2018. Scientific Evidence and Recommendations for Managing PFAS Contamination in Michigan. December 7, 2018. Available online at: https://www.michigan.gov/documents/pfasresponse/Science_Advisory_Board_Report_641294_7.pdf

Midasch O, Drexler H, Hart N, et al. 2007. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: A pilot study. Int Arch Occup Environ Health 80:643-648.

Minnesota Department of Health. 2018 - Toxicological Summary for: Perfluorooctanoate: http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfoa.pdf

Minnesota Department of Health. 2019 - Toxicological Summary for: Perfluorooctane sulfonate: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf

Minnesota Department of Health. 2019 - Toxicological Summary for: Perfluorohexane sulfonate: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf

Monroy R, Morrison K, Teo K, et al. 2008. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ Res 108:56-62.

Moriwaki H, et al. 2003. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes. J. Environ. Monit., 5, 753-757.

Nakayama SF, et al. 2019. Worldwide trends in tracing poly- and perfluoroalkyl substances (PFAS) in the environment. Trends in Analytical Chemistry. Article in press, available online 2/14/19.

Nascimento RA, Nunoo DBO, Bizkarguenaga E, Schultes L, Zabaleta I, Benskin JP, Spanó S, Leonel J. 2018. Sulfluramid use in Brazilian agriculture: A source of per- and polyfluoroalkyl substances (PFASs) to the environment. Environ Pollut. 242(Pt B):1436-1443. doi: 10.1016/j.envpol.2018.07.122.

Needham LL, Grandjean P, Heinzow B, et al. 2011. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ Sci Technol 45(3):1121-1126.

Negri E, et al. 2017. Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data. Critical Reviews in Toxicology 47: 482-508.

New Hampshire Department of Environmental Services (NHDES). 2019. Summary Report on the New Hampshire Department of Environmental Services Development of Maximum Contaminant Levels and Ambient Groundwater Quality Standards for Perfluorooctanesulfonic Acid (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorononanoic Acid (PFNA), And Perfluorohexanesulfonic Acid (PFHxS). Available at: https://www.des.nh.gov/organization/commissioner/pip/publications/documents/r-wd-19-01.pdf

Nian M, Li QQ, Bloom M, Qian ZM, Syberg KM, Vaughn MG, Wang SQ, Wei Q, Zeeshan M, Gurram N, Chu C, Wang J, Tian YP, Hu LW, Liu KK, Yang BY, Liu RQ, Feng D, Zeng XW, Dong GH. 2019. Liver function biomarkers disorder is associated with exposure to perfluoroalkyl acids in adults: Isomers of C8 Health Project in China. Environ Res. 172:81-88. doi: 10.1016/j.envres.2019.02.013.

NJ DWQI 2017: NJ Drinking Water Quality Institute (DWQI). 2016. Health-Based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA). Available online at: https://www.state.nj.us/dep/watersupply/pdf/pfoa-appendixa.pdf

NJ DWQI 2018: NJ Drinking Water Quality Institute (DWQI). 2018. Health-Based Maximum Contaminant Level Support Document: Perfluorononanoic Acid (PFNA). Available online at: https://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf

NJ DWQI 2018: NJ Drinking Water Quality Institute (DWQI). 2018. Health-Based Maximum Contaminant Level Support Document: Perfluorooctane Sulfonate (PFOS). Available online at: https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf

New York Department of Health (NYDOH), 2018 presentation and professional communications. Presentation available at: https://www.health.ny.gov/environmental/water/drinking/dwqc/

NTP 2016: National Toxicology Program. NTP Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate. September 2016.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115(9):1298–1305, PMID: 17805419, 10.1289/ehp.10009.

Onishchenko N, Fischer C, Wan Ibrahim WN, et al. 2011. Prenatal exposure to PFOS or PFOA altersmotor function in mice in a sex-related manner. Neurotox Res 19(3):452-461.

Perkins RG, Butenhoff JL, Kennedy GL, et al. 2004. 13-Week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drug Chem Toxicol 27(4):361-378.

Porpora MG, Lucchini R, Abballe A, et al. 2013. Placental transfer of persistent organic pollutants: A preliminary study on mother-newborn pairs. Int J Environ Res Public Health 10(2):699-711.

Post GB, Gleason JA, Cooper KR. 2017. Key scientific issues in developing drinking water guidelines for perfluoroalkyl acids: Contaminants of emerging concern. PLoS Biol. 15(12):e2002855. doi: 10.1371/journal.pbio.2002855.

Quist EM, Filgo AJ, Cummings CA, et al. 2015a. Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). Toxicol Pathol 43(4):546-557. 10.1177/0192623314551841.

Quist EM, Filgo AJ, Cummings CA, et al. 2015b. Supplemental data: Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). (Toxicol Pathol 43(4):546-557). Toxicol Pathol 43:546-557.

Ramhoj L, et al. 2018. Perfluorohexane Sulfonate (PFHxS) and a Mixture of Endocrine Disrupters Reduce Thyroxine Levels and Cause Antiandrogenic Effects in Rats. Toxicological Sciences, 163(2), 579-591.

Rappazzo KM, et al. 2017. Exposure to Perfluorinated Alkyl Substances and Health Outcomes in Children: A Systematic Review of the Epidemiologic Literature. International Journal of Environmental Research and Public Health, 14, 691.

Rebholz SL, Jones T, Herrick RL, et al. 2016. Hypercholesterolemia with consumption of PFOA-laced Western diets is dependent on strain and sex of mice. Toxicology reports 3:46-54. 10.1016/j.toxrep.2015.11.004.

Rogers JM, Ellis-Hutchings RG, Grey BE, et al. 2014. Elevated blood pressure in offspring of rats exposed to diverse chemicals during pregnancy. Toxicol Sci 137(2):436-446. 10.1093/toxsci/kft248.

Rosen MB, Abbott BD, Wolf DC, et al. 2008a. Gene profiling in the livers of wild-type and PPARα-null mice exposed to perfluorooctanoic acid. Toxicol Pathol 36(4):592-607.

Rosen MB, Das KP, Rooney J, et al. 2017. PPARα-independent transcriptional targets of perfluoroalkyl acids revealed by transcript profiling. Toxicology Toxicology. 15;387:95-107. doi: 10.1016/j.tox.2017.05.013.

Rosen MB, Lee JS, Ren H, et al. 2008b. Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: Evidence for the involvement of nuclear receptors PPARα and CAR. Toxicol Sci 103(1):46-56.

Rosen MB, Thibodeaux JR, Wood CR, et al. 2007. Gene expression profiling in the lung and liver of PFOA-exposed mouse fetuses. Toxicology 239:15-33.

Schaider LA, et al. 2017. Fluorinated Compounds in U.S. Fast Food Packaging. Environmental Science & Technology Letters, 4, 105-111.

Scher DP, Kelly JE, Huset CA, Barry KM, Hoffbeck RW, Yingling VL, Messing RB. 2018. Occurrence of perfluoroalkyl substances (PFAS) in garden produce at homes with a history of PFAS-contaminated drinking water. Chemosphere. 196:548-555. doi: 10.1016/j.chemosphere.2017.12.179.

Son H, Kim S, Shin HI, et al. 2008. Perfluorooctanoic acid-induced hepatic toxicity following 21-day oral exposure in mice. Arch Toxicol 82:239-246.

Stein CR, McGovern KJ, Pajak AM, et al. 2016. Perfluoroalkyl and polyfluoroalkyl substances and indicators of immune function in children aged 12-19 y: National Health and Nutrition Examination Survey. Pediatr Res 79(2):348-357.

Suh KS, et al. 2017. Perfluorooctanoic acid induces oxidative damage and mitochondrial dysfunction in pancreatic β-cells. Mol Med Rep. 15(6): 3871-3878.

Sundström M, Chang SC, Noker PE, et al. 2012. Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. Reprod Toxicol 33(4):441-451.

Tan X, Xie G, Sun X, et al. 2013. High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways. PLoS ONE 8(4):e61409.

Texas Commission on Environmental Quality (TCEQ). 2016. Perfluorocompounds (PFCs). Available online at: https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf

Thibodeaux JR, Hanson RG, Rogers JM, et al. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: Maternal and prenatal evaluations. Toxicol Sci 74(2):369-381.

Thomford PJ. 2001. 4-Week capsule toxicity study with ammonium perfluorooctanoate (APFO) in Cynomolgus monkeys. APME Ad-Hoc APFO toxicology working group.

Thompson J, Lorber M, Toms LM, et al. 2010. Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid. Environ Int 36(4):390-397. 10.1016/j.envint.2010.02.008.

Trudel D, et al. 2008. Estimating Consumer Exposure to PFOS and PFOA. Risk Analysis, 28(2), 251-269. Erratum issued, 2008. Risk Analysis, 28(3), 807.

Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbuheler K. 2008. Estimating consumer exposure to PFOS and PFOA. Risk Anal. 28: 251-269.

Tucker DK, Macon MB, Strynar MJ, et al. 2015. The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. Reprod Toxicol 54:26-36. 10.1016/j.reprotox.2014.12.002.

Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S (October 2011). "The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases". J Adv Pharm Technol Res. 2(4): 236–40.

USEPA (U.S. Environmental Protection Agency). 2000. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Documents. Accessed online at: https://www.epa.gov/wqc/methodology-deriving-ambient-water-quality-criteria-protection-human-health-2000-documents

USEPA (U.S. Environmental Protection Agency). 2002. A Review of the Reference Dose and Reference Concentration Processes. EPA/630/P-02/0002F. Risk Assessment Forum, Washington, DC. Accessed online at: https://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes

USEPA (U.S. Environmental Protection Agency). 2011. Exposure Factors Handbook: 2011 Edition. EPA/600/R-090/052F. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. 1436 pp. Accessed online at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

USEPA (U.S. Environmental Protection Agency). Benchmark Dose Technical Guidance. Document # EPA/100/R-12/001. June 2012. Accessed online at: https://www.epa.gov/risk/benchmark-dose-technical-guidance

USEPA (U.S. Environmental Protection Agency). 2016a. Health Effects Support Document for Perfluorooctanoic acid (PFOA). Document # EPA 822-R-16-003. May 2016. Accessed online at: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final_508.pdf

USEPA (U.S. Environmental Protection Agency). 2016b. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). Document # EPA 822-R-16-002. May 2016. Accessed online at: https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf

USEPA (U.S. Environmental Protection Agency). 2019. Exposure Factors Handbook: Chapter 3 Update. EPA/600/R-090/052F. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. Accessed online at: https://www.epa.gov/sites/production/files/2019-02/documents/efh_-_chapter_3_update.pdf

Vanden Heuvel JP, Thompson JT, Frame SR, et al. 2006. Differential activation of nuclear receptors by perfluorinated fatty acid analogs and natural fatty acids: A comparison of human, mouse, and rat peroxisome proliferator-activated receptor-α, -ß, and -γ, liver x receptor-ß, and retinoid x receptor-α. Toxicol Sci 92(2):476-489.

Vélez MP, Arbuckle TE, Fraser WD. 2015. Maternal exposure to perfluorinated chemicals and reduced fecundity: The MIREC study. Hum Reprod 30(3):701-709. 10.1093/humrep/deu350.

Verner MA, Loccisano AE, Morken NH, et al. 2015. Associations of perfluoroalkyl substances (PFAS) with lower birth weight: An evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK). Environ Health Perspect 123(12):1317-1324.

Viberg H, Lee I, Eriksson P. 2013. Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. Toxicology 304:185-191.

Vieira VM, Hoffman K, Shin M, et al. 2013. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis. Environ Health Perspect 121(3):318-323.

Wan HT, Zhao YG, Leung PY, et al. 2014b. Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. PLoS ONE 9(1):e87137. 10.1371/journal.pone.0087137.

Wang H, Du H, Yang J, Jiang H, O K, Xu L, Liu S, Yi J, Qian X, Chen Y, Jiang Q, He G. 2019. S, PFOA, estrogen homeostasis, and birth size in Chinese infants. Chemosphere. 221:349-355. doi: 10.1016/j.chemosphere.2019.01.061.

Wang J, Yan S, Zhang W, et al. 2015. Integrated proteomic and miRNA transcriptional analysis reveals the hepatotoxicity mechanism of PFNA exposure in mice. J Proteome Res 14(1):330-341. 10.1021/pr500641b.

Washburn ST, et al. 2005. Exposure assessment and risk characterization for perfluorooctanoate in selected consumer articles. Environmental Science & Technology, 39(11), 3904-10.

White SS, Calafat AM, Kuklenyik Z, et al. 2007. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. Toxicol Sci 96(1):133-144.

White SS, Kato K, Jia LT, et al. 2009. Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. Reprod Toxicol 27(3-4):289-298.

White SS, Stanko JP, Kato K, et al. 2011. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. Environ Health Perspect 119(8):1070-1076.

WHO. e-Library of Evidence for Nutrition Actions (eLENA). 2019. Exclusive breastfeeding for optimal growth, development and health of infants. Available online at: https://www.who.int/elena/titles/exclusive_breastfeeding/en/

Winkens K, et al. 2017. Early life exposure to per- and polyfluoroalkyl substances (PFASs): A critical review. Emerging Contaminants, 3, 55-68.

Winkens K, et al. 2018. Perfluoroalkyl acids and their precursors in floor dust of children's bedrooms – Implications for indoor exposure. Environment International, 119, 493-502.

Winkens K, Giovanoulis G, Koponen J, Vestergren R, Berger U, Karvonen AM, Pekkanen J, Kiviranta H, Cousins IT. 2018. Perfluoroalkyl acids and their precursors in floor dust of children's bedrooms - Implications for indoor exposure. Environ Int. 119:493-502. doi: 10.1016/j.envint.2018.06.009.

Wolf CJ, Fenton SE, Schmid JE, et al. 2007. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. Toxicol Sci 95(2):462-473.

Wolf CJ, Schmid JE, Lau C, et al. 2012. Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARa) by perfluoroalkyl acids (PFAAs): Further investigation of C4-C12 compounds. Reprod Toxicol 33:546-551.

Wolf CJ, Takacs ML, Schmid JE, et al. 2008. Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol Sci 106(1):162-171.

Wolf CJ, Zehr RD, Schmid JE, et al. 2010. Developmental effects of perfluorononanoic Acid in themouse are dependent on peroxisome proliferator-activated receptor-alpha. PPAR Res 2010 10.1155/2010/282896.

Worley RR, Yang X, Fisher J. 2017. Physiologically based pharmacokinetic modeling of human exposure to perfluorooctanoic acid suggests historical non drinking-water exposures are important for predicting current serum concentrations. Toxicol Appl Pharmacol. 330:9-21. doi: 10.1016/j.taap.2017.07.001.

Yahia D, El-Nasser MA, Abedel-Latif M, et al. 2010. Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction. J Toxicol Sci 35(4):527-533.

Yahia D, Tsukuba C, Yoshida M, et al. 2008. Neonatal death of mice treated with perfluorooctane sulfonate. J Toxicol Sci 33(2):219-226.

Yang L, Wang Z, Shi Y, et al. 2016. Human placental transfer of perfluoroalkyl acid precursors: Levels and profiles in paired maternal and cord serum. Chemosphere 144:1631-1638. 10.1016/j.chemosphere.2015.10.063.

Zeng HC, Li YY, Zhang L, et al. 2011. Prenatal exposure to perfluorooctanesulfonate in rat resulted in long-lasting changes of expression of synapsins and synaptophysin. Synapse 65(3): 225-33.

Zeng XW, Bloom MS, Dharmage SC, Lodge CJ, Chen D, Li S, Guo Y, Roponen M, Jalava P, Hirvonen MR, Ma H, Hao YT, Chen W, Yang M, Chu C, Li QQ, Hu LW, Liu KK, Yang BY, Liu S, Fu C, Dong GH. 2019. Prenatal exposure to perfluoroalkyl substances is associated with lower hand, foot and mouth disease viruses antibody response in infancy: Findings from the Guangzhou Birth Cohort Study. Sci Total Environ. 663:60-67. doi: 10.1016/j.scitotenv.2019.01.325.

Zhang T, Sun H, Lin Y, Qin X, Zhang Y, Geng X, Kannan K. 2013. Distribution of poly- and perfluoroalkyl substances in matched samples from pregnant women and carbon chain length related maternal transfer. Environ Sci Technol. 47(14):7974-81. doi: 10.1021/es400937y.

Zhang Y, Beesoon S, Zhu L, et al. 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol 47(18):10619-10627. 10.1021/es401905e.

Zhu Y, Qin XD, Zeng XW, et al. 2016. Associations of serum perfluoroalkyl acid levels with T-helper cell-specific cytokines in children: By gender and asthma status. Sci Total Environ 559:166-173. 10.1016/j.scitotenv.2016.03.187.