PFAS Health, Toxicology Regulatory Subgroup Meeting

Virginia Department of Health Office of Drinking Water
(Discuss States with PFOA MCLs)
March 12, 2021
1:30pm – 3:30pm

PFAS Health & Toxicology Subgroup

Final Meeting Minutes

WebEx, Office of Drinking Water, 109 Governor Street 6th Floor, Richmond, VA 23219

1. Opening Remarks

VDH State Toxicologist, Dwight Flammia, Ph.D. called the meeting to order 1:32 p.m. The meeting was conducted by electronic communication means (WebEx) due to the ongoing public health emergency associated with the coronavirus pandemic. The meeting was recorded. Minutes and materials provided to Subgroup members will be posted on Town Hall.

2. Subgroup Members Present:
   Kelly Ryan (Va American Water)
   David Jurgens (City of Chesapeake)
   Erin Reilly (James River Association)
   Steve Risotto (ACC)
   Benjamin Hollard (DEQ)
   Dwight Flammia (VDA, State Toxicologist)
   Steve Herzog (Hanover County)
   Paul Nyffeler (Chem Law)

   Guests:
   Anna Killius
   Joe DiNardo
   Bill Mann
   Ryan Hanson

   ODW Staff:
   Kris Latino

3. Review of previous meeting

The Subgroup determined that there were no changes to minutes from the February 12, 2021 meetings. The minutes and other meeting materials will be posted on Town Hall as "Final."

4. Presentation

The goal of this meeting was to discuss perfluorooctanoic acid (PFOA) toxicology by looking at the states that have adopted a maximum contaminant limit (MCL) for PFOA and the different ways each state developed their plans.

Dwight used a PowerPoint presentation (attached) to go through details about the methods each state with an MCL for PFOA used to develop their conclusions. Copies of the papers cited in the attached presentation are available for Subgroup members on the PFAS Workgroup's SharePoint site.

Currently only a few states have developed PFOA MCLs. They include:

Massachusetts	20 ppt (sum of the PFAS not to exceed)
Michigan	8 ppt
New Hampshire	12 ppt
New Jersey	14 ppt
New York	10 ppt
Vermont	20 ppt (sum of PFAS not to exceed)

5. Discussion

VDH has contracted with Old Dominion University (ODU) to perform a literature review for the PFAS Workgroup and to support the requirements in HB586 (2020). Dwight has asked the Subgroup to provide a list of information for ODW to look for as part of the literature review.

Subgroup members suggested the following topics should be included (if information is available):

- Relative source contribution, water ingestion rate, EPS RSC flowchart, contribution from non-drinking water
- Toxicokinetics – DAF, absorption, volume of distribution, serum, ½ lives between compounds, which ½ life is used – male or females.
- Animal models – rats vs. mice vs. etc.
- NHANES Studies
- History of use of uncertainty factors and modifying factors (database)
- Are vulnerable subpopulations identified in the report (particularly ATSDR)
- ATSDR did assign MCL to PFOA – no chronic data
- PFAS effect on immune response – without more people getting sick – is that an adverse effect?
- What makes an adverse effect (NOEL vs NOAEL)
- No effect vs. no adverse effect when developing MCLs
- Half-life of compounds

- Relative source distribution – what is appropriate.
- Contributions from non-water sources?
- Information from the Navy, Chesapeake and Chincoteague

Dwight will follow up with ODU on these suggestions.

Paul Nyffeler has also provided a "Draft Priorities for Information from This Subgroup." Dwight asked Subgroup members to review the "Draft Priorities" and provide feedback (suggestions and/or comments) prior to the next Subgroup meeting in April. A copy of the "Draft Priorities" follows the meeting minutes. It is also saved on SharePoint.

If Subgroup members have additional recommendations related to ODU's literature review, please contact Dwight directly.

Dwight said he would prefer to gather information on perfluorooctane sulfonate (PFOS – discussed at the Subgroup's February meeting) and PFOA before adding another compound. He feels it might be better to wait and see the ODU work before deciding to focus elsewhere. After we get data, we can work together to see what we should present to PFAS workgroup.

6. Public Comment

Bill Mann had a question regarding the New York discussion. He asked if there is some impact with feasibility and costs. Dwight explained that the Subgroup would need to recommend an MCLG. Then the information would be passed on to another group to consider and develop a recommendation for the MCL.

7. Closing items

Dwight concluded the meeting at 3:30 pm. The next meeting is scheduled for April 9, 2021 from 1:30 to 3:30.

PFAS Health, Toxicology Regulatory Subgroup Meeting

Virginia Department of Health Office of Drinking Water
(Discuss States with PFOA MCLs)
March 12, 2021
1:30pm – 3:30pm

Opening Remarks

Member Roll Call

Review of Previous Meeting Minutes

Presentation

Discussion

Public Comment

Closing items

Virginia Department of Health
PFAS Health & Toxicology Subgroup

DRAFT PRIORITIES FOR INFORMATION FROM THIS SUBGROUP

The following are information, values, findings, recommendations, and/or conclusions that the PFAS Health & Toxicology Subgroup is considering reaching or making as part of the process for creating recommendations as necessary for Maximum Contaminant Levels (MCLs) for Per- and PolyFluoroAlkyl Substances (PFAS) in drinking water.

- Maximum Contaminant Level Goals for individual PFAS
- Understanding of toxicological effects of PFAS
    - Liver
    - Kidney
    - Regulatory/Hormone/Serum cholesterol levels (and associations between exposure to PFAS and cardiovascular disease, diabetes, obesity, metabolic syndrome, etc.)
    - Immune response/immunotoxicity
    - Memory gland development
    - Teratogenicity
    - Carcinogenicity
- Values of lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL) for toxicological effects
- Whether toxicological studies or results were conducted or found in animals or humans

- Reference sources considered, including specific references relied upon for toxicological effects, observed levels, and species subjects
- Drinking water intake for nursing mothers
- Whether to treat before PFAS compounds assessed by EFSA or other states as a group based on similar human clearance half-lives?
    - In other words, is it reasonable to assume that extended presence of compounds in body is associated with harm?
- Is it reasonable to propose an MCLG for a given PFAS based on toxicity in nursing infants that applies the average clearance rates in male and female humans if women exhibit higher clearance rates and males have no role in fetal development and lactation?
- If the gender difference in PFAS clearance exists in both human adults and infants, should the MCLG be directed at the combination of the clearance rate of a female adult and a male infant to account for the gender differences?
- Should the PFAS Occurrence Subgroup assess the presence of PFAS in foods consumed by Virginians to assist in ascertaining the relative source contribution of PFAS sources other than drinking water in Virginia (as opposed to national data)?
- When assessing effects on different biological areas (kidney, liver, cholesterol), whether the observed affects are actual or statistically significant health impacts or health risks.

    - For example, there is evidence that the elevated levels of cholesterol associated with some of these compounds does not cause a statistically significant increase in heart disease in humans.

- When considering PFAS occurrence data, should the blood concentrations of PFAS in Virginians be considered? In other words, if a specific PFAS compound is found in Virginia drinking water but it is not detected in the blood of Virginians (when using an assay that is capable of detecting its presence), should this absence of data affect the need to regulate that PFAS in drinking water?

Establishing Regulatory Limits for PFAS in Virginia Drinking Water

PFAS Toxicology Regulatory Workgroup

Dwight Flammia, Ph.D.
State Public Health Toxicologist
Virginia Department of Health

March 12, 2021

Introductions

Jillian Terhune (City of Norfolk)
Kelly Ryan (VA American Water)
Mark Estes (Halifax County Service Authority)
David Jurgens (City of Chesapeake)
Erin Reilly (James River Association)
Chris Leyen (VCLV)
Steve Risotto (ACC)
Benjamin Holland (DEQ)*
Dwight Flammia (VDH, State Toxicologist)
Andrea Wortzel (Mission H2O)
Steve Herzog (Hanover County)
Paul Nyffeler (Chem Law)

PFAS Workgroup Meeting Overview

Meeting Overview

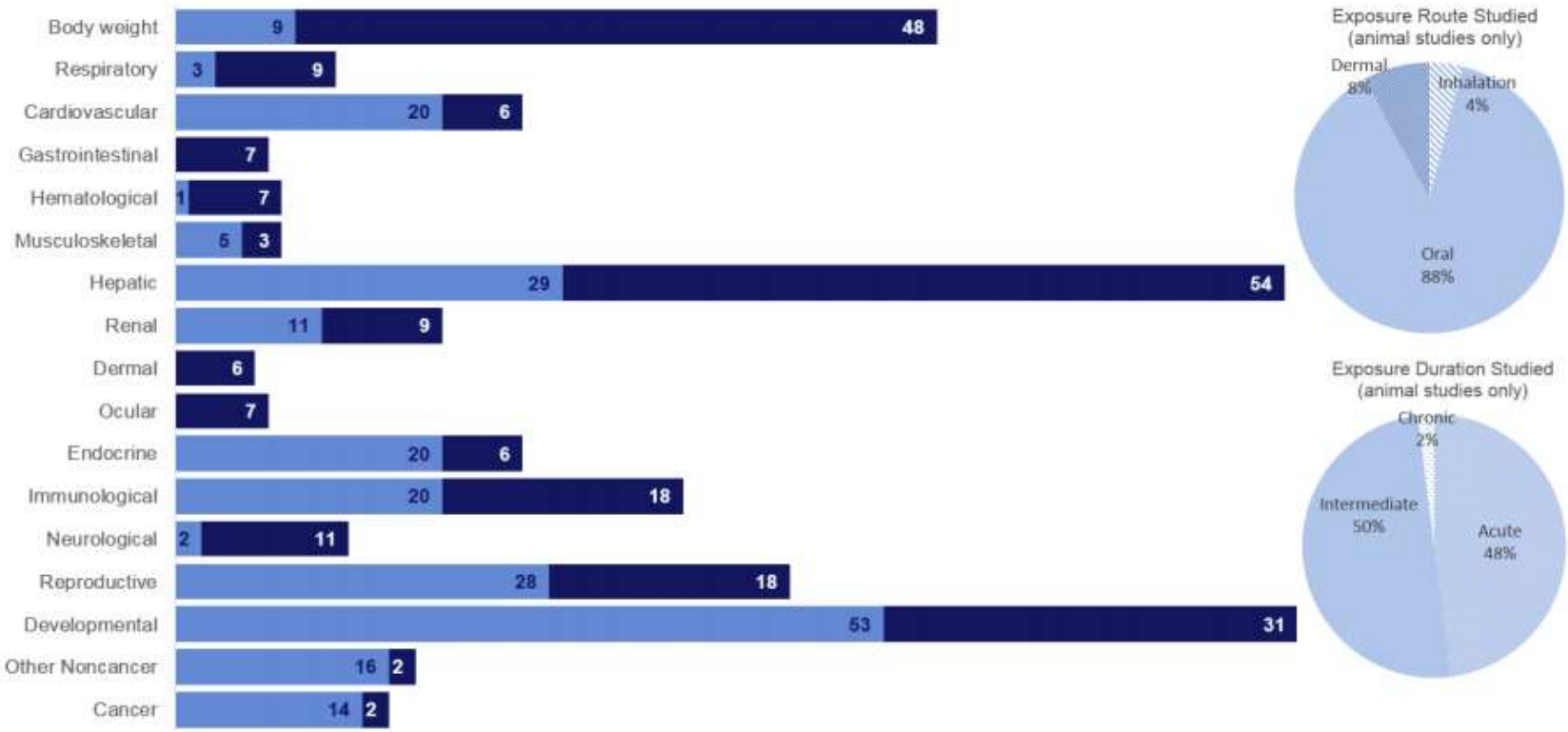
- Opening Remarks
- Review of previous meeting
- Workgroup Members Introductions
- Presentation
- Discussion
- Assignments
- Public Comment
- Next Meeting

States with PFOA MCLs

• Massachusetts	• 20 ppt (sum of five PFAS not to exceed)
• Michigan	• 8 ppt
• New Hampshire	• 12 ppt
• New Jersey	• 14 ppt
• New York	• 10 ppt
• Vermont	• 20 ppt (sum of five PFAS not to exceed)

Figure 2-1. Overview of the Number of Studies Examining PFOA Health Effects*

Developmental, hepatic, and body weight effects of PFOA were the most widely examined potential toxicity outcomes
More studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 271 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints. In this figure, the number of human studies is referring to the number of publications.

Figure 2-6. Levels of Significant Exposure to PFOA – Oral
Acute (≤14 days)

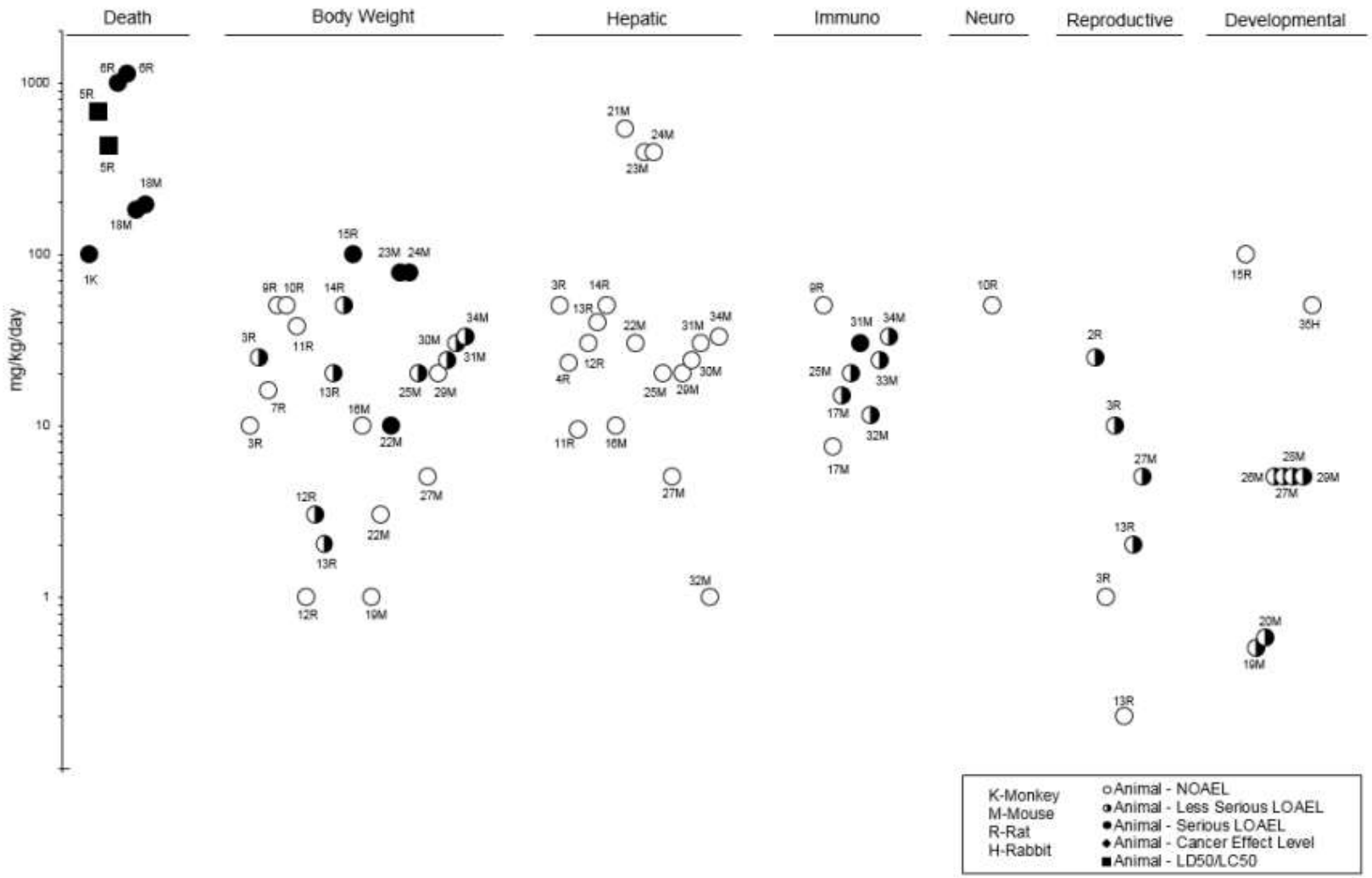


Figure 2-6. Levels of Significant Exposure to PFOA – Oral

Intermediate (15–364 days)

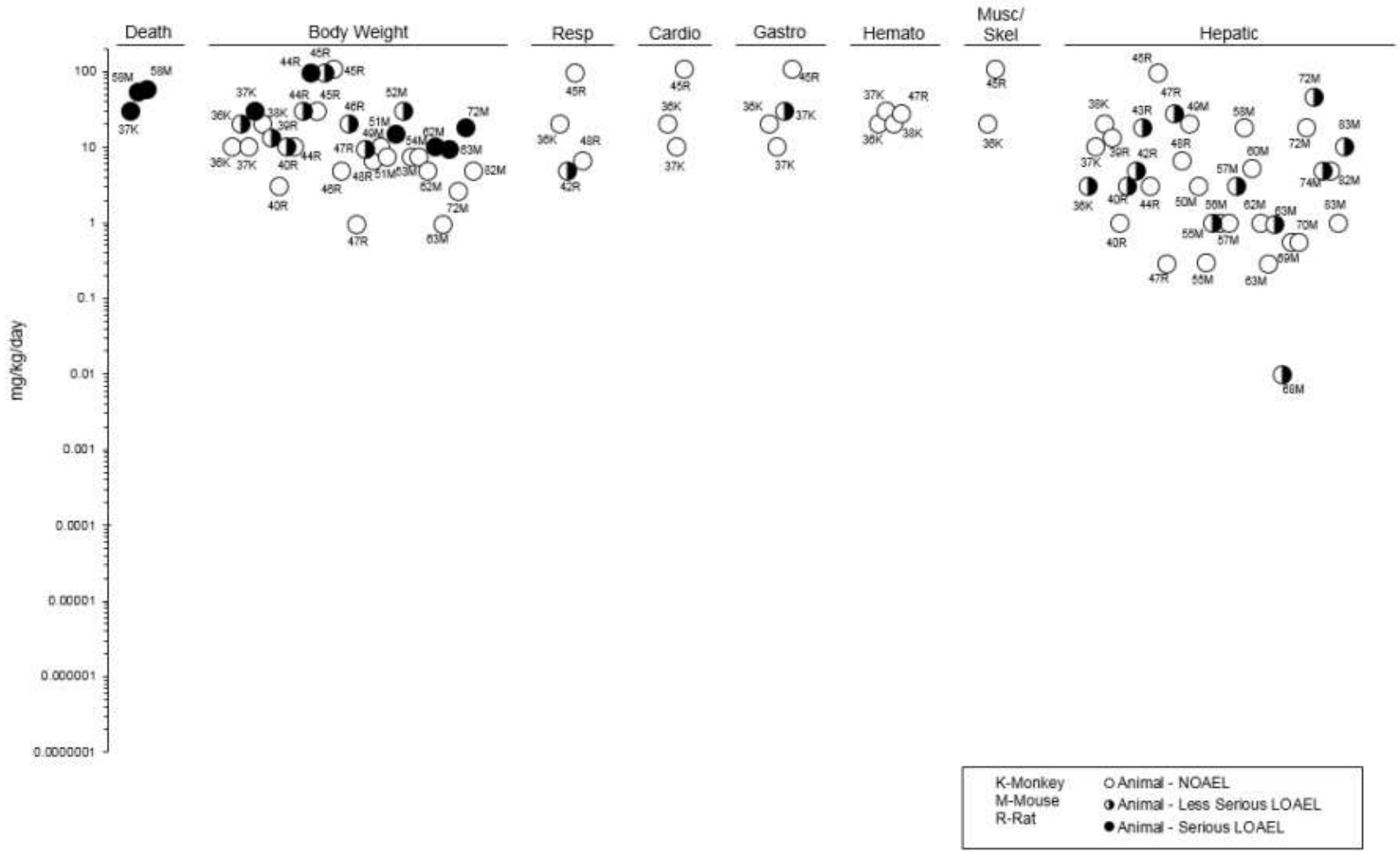


Figure 2-6. Levels of Significant Exposure to PFOA – Oral
Intermediate (15–364 days)

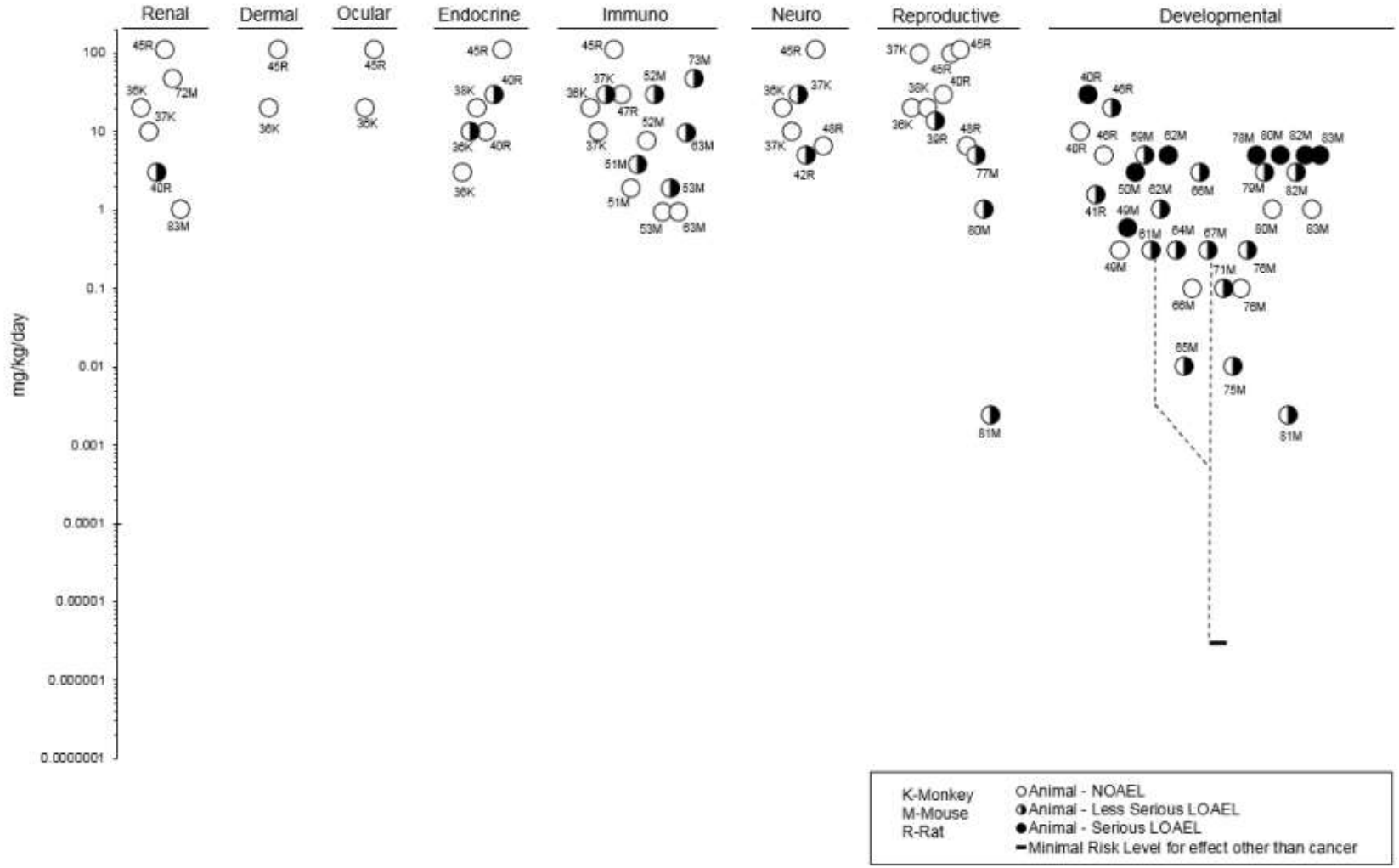
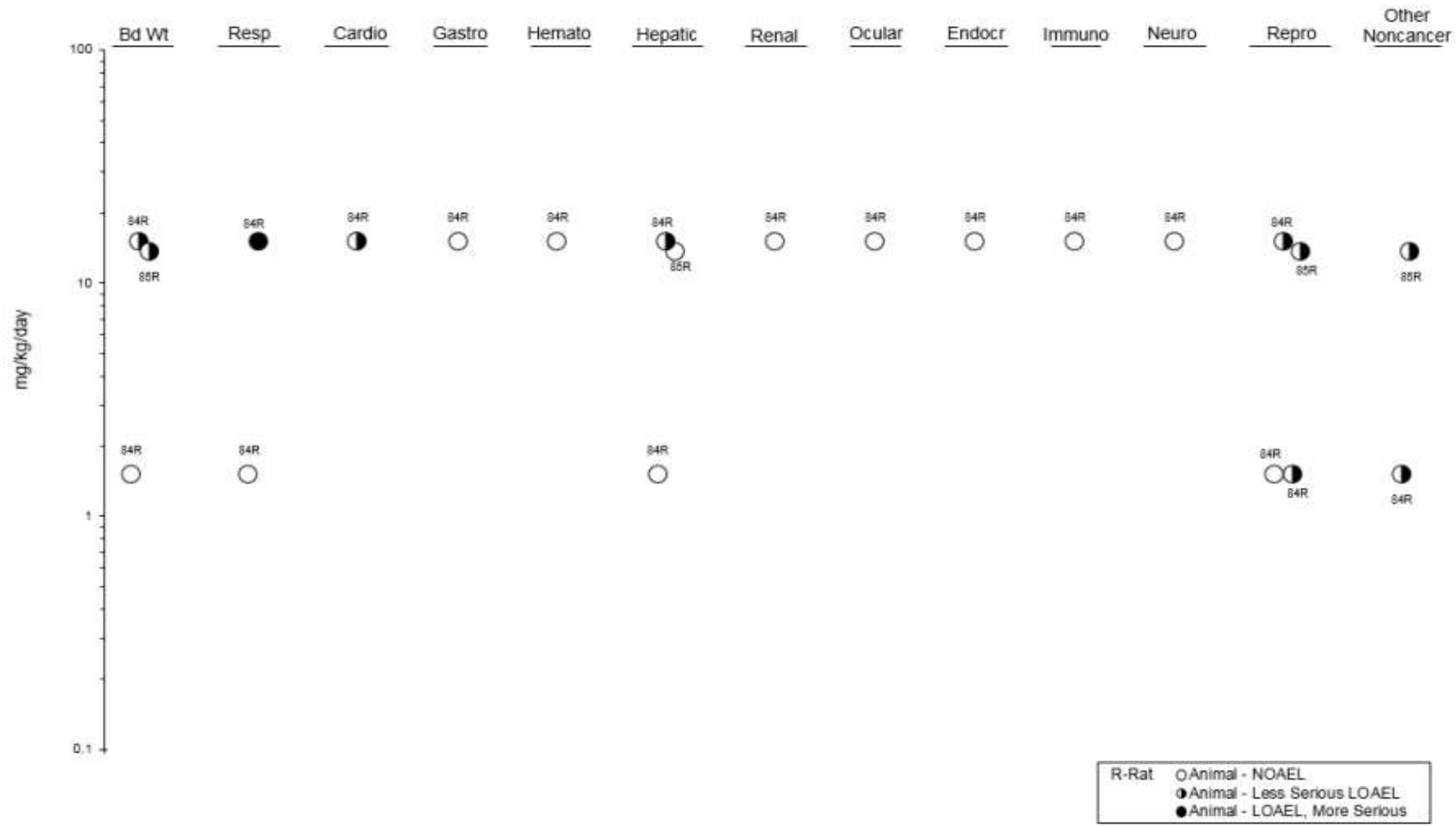


Figure 2-6. Levels of Significant Exposure to PFOA – Oral
Chronic (≥365 days)



Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse

Christopher Lau,*,[1] Julie R. Thibodeaux,* Roger G. Hanson,* Michael G. Narotsky,* John M. Rogers,* Andrew B. Lindstrom,† and Mark J. Strynar†

Reproductive Toxicology Division, National Health and Environmental Effects Research Laboratory, and †Human Exposure and Atmospheric Science Division, National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Perfluorooctanoic acid (PFOA), a member of the perfluoroalkyl acids that have wide commercial applications, has recently been detected in humans and wildlife. The current study characterizes the developmental toxicity of PFOA in the mouse. Timed-pregnant CD-1 mice were given 1, 3, 5, 10, 20, or 40 mg/kg PFOA by oral gavage daily from gestational day (GD) 1 to 17; controls received an equivalent volume (10 ml/kg) of water. PFOA treatment produced dose-dependent full-litter resorptions; all dams in the 40-mg/kg group resorbed their litters. Weight gain in dams that carried pregnancy to term was significantly lower in the 20-mg/kg group. At GD 18, some dams were sacrificed for maternal and fetal examinations (group A), and the rest were treated once more with PFOA and allowed to give birth (group B). Postnatal survival, growth, and development of the offspring were monitored. PFOA induced enlarged liver in group A dams at all dosages, but did not alter the number of implantations. The percent of live fetuses was lower only in the 20-mg/kg group (74 vs. 94% in controls), and fetal weight was also significantly lower in this group. However, no significant increase in malformations was noted in any treatment group. The incidence of live birth in group B mice was significantly lowered by PFOA: ca. 70% for the 10- and 20-mg/kg groups compared to 96% for controls. Postnatal survival was severely compromised at 10 or 20 mg/kg, and moderately so at 5 mg/kg. Dose-dependent growth deficits were detected in all PFOA-treated litters except the 1-mg/kg group. Significant delays in eye-opening (up to 2–3 days) were noted at 5 mg/kg and higher dosages. Accelerated sexual maturation was observed in male offspring, but not in females. These data indicate maternal and

Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse

Christopher Lau,*,[1] Julie R. Thibodeaux,* Roger G. Hanson,* Michael G. Narotsky,* John M. Rogers,* Andrew B. Lindstrom,† and Mark J. Strynar†

Reproductive Toxicology Division, National Health and Environmental Effects Research Laboratory, and †Human Exposure and Atmospheric Science Division, National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

LOAEL identified - Male and female pup ossification and accelerated male puberty.

RfD was calculated from serum levels

Species	Study Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Critical Effect(s)	Reference
Female	17 (pups) /18 (dams) days	none	1	↑ absolute maternal liver weight, ↓ ossification (calvarin, enlarged fontanel), accelerated onset of puberty in male offspring.	Lau et al. 2006

Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO)

Scott E. Loveless [a,*], Carol Finlay [a], Nancy E. Everds [a], Steven R. Frame [a], Peter J. Gillies [b], John C. O'Connor [a], Charles R. Powley [a], Gerald L. Kennedy [a]

[a] *DuPont Haskell Laboratory for Health and Environmental Sciences, Newark, DE 19714, United States*
[b] *DuPont Nutrition and Health, Newark, DE 19714, United States*

Received 21 November 2005; received in revised form 3 January 2006; accepted 4 January 2006
Available online 31 January 2006

The purpose of this study was to compare the toxicity of linear/branched ammonium perfluorooctanoate (APFO) with that of linear and branched APFO. Linear/branched APFO (approximately 80% linear and 20% branched isomers) was formerly used in the production of commercial products. The extensive toxicologic database for APFO has been developed essentially using this mixture of isomers. The trend now is to use APFO containing only the linear isomer. The current study was performed to determine if the toxicological database developed for the linear/branched isomer is applicable to the linear isomer. To determine the contribution of branched APFO to the toxicity of linear/branched APFO, a form of APFO that was 100% branched was synthesized. Rats and mice were given doses by oral gavage ranging from 0.3 to 30 mg/kg of either the linear/branched, linear, or branched APFO for 14 days. Clinical signs, body weights, food consumption, selected hematology and serum lipid parameters, liver and kidney weights, hepatic peroxisomal β-oxidation, and serum PFOA concentrations were evaluated. Mean body weights were about 20% lower in rats and mice dosed with 30 mg/kg of linear/branched or linear APFO compared to controls, and 3–5% lower in animals dosed with 30 mg/kg of branched APFO. In rats, all three forms reduced lipids. In mice, all three forms reduced total and HDL cholesterol similarly but triglycerides were increased at lower doses. Increased peroxisomal β-oxidation activity and serum PFOA concentrations were seen in both species but these effects were least pronounced in rats dosed with the branched material. In rats, serum PFOA levels were 20–51 ppm at Lowest Observed Effect Levels (LOEL) of 0.3–1 mg/kg, based primarily upon lipid parameters. In mice, serum PFOA levels were 10–14 ppm at the LOEL of 0.3 mg/kg, based primarily upon relative liver weight. In both rats and mice, the overall responses to the linear/branched and the linear forms of PFOA were similar, but the branched form appears to be less potent. Based on these results, and for the endpoints evaluated in this study, the toxicological database developed primarily from testing linear/branched APFO is applicable to linear APFO.

Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation

A. Koskela [a,*], M.A. Finnilä [b], M. Korkalainen [c], S. Spulber [d], J. Koponen [c], H. Håkansson [e], J. Tuukkanen [a], M. Viluksela [c,f]

[a] Institute of Cancer Research and Translational Medicine, MRC Oulu and Department of Anatomy and Cell Biology, Faculty of Medicine, University of Oulu, Oulu, Finland
[b] Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland
[c] National Institute for Health and Welfare, Department of Health Protection, Kuopio, Finland
[d] Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
[e] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[f] Department of Environmental and Biological Sciences, University of Eastern Finland, Kuopio, Finland

Perfluorooctanoic acid (PFOA) is a ubiquitous and persistent environmental chemical, which has been used extensively due to its stability and surface tension-lowering properties. Toxicological effects include induction of neonatal mortality and reproductive toxicity. In this study, pregnant C57BL/6 mice were exposed orally to 0.3 mg PFOA/kg/day throughout pregnancy, and female offspring were studied at the age of 13 or 17 months. Morphometrical and biomechanical properties of femurs and tibias were analyzed with micro-computed tomography and 3-point bending, and bone PFOA concentrations were determined by mass spectrometry. The effects of PFOA on bone cell differentiation were studied in osteoclasts from C57BL/6 mice and in the MC3T3 pre-osteoblast cell line. PFOA exposed mice showed increased femoral periosteal area as well as decreased mineral density of tibias. Biomechanical properties of these bones were not affected. Bone PFOA concentrations were clearly elevated even at the age of 17 months. In osteoblasts, low concentrations of PFOA increased osteocalcin (OCN) expression and calcium secretion, but at PFOA concentrations of 100 μM and above osteocalcin (OCN) expression and calcium secretion were decreased. The number of osteoclasts was increased at all PFOA concentrations tested and resorption activity dose-dependently increased from 0.1–1.0 μM, but decreased at higher concentrations. The results show that PFOA accumulates in bone and is present in bones until the old age. PFOA has the potential to influence bone turnover over a long period of time. Therefore bone is a target tissue for PFOA, and altered bone geometry and mineral density seem to persist throughout the life of the animal.

Prenatal Exposure to PFOS or PFOA Alters Motor Function in Mice in a Sex-Related Manner

Natalia Onishchenko · Celia Fischer · Wan Norhamidah Wan Ibrahim · Sara Negri · Stefan Spulber · Danilo Cottica · Sandra Ceccatelli

Abstract Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are organic surfactants widely used in various industrial and consumer applications. Due to their chemical properties, these perfluorinated compounds (PFCs) have also become persistent contaminants. The risk of possible intrauterine and lactational exposure to these chemicals poses a significant health concern for potential developmental effects. In the present study we have found that dietary exposure of mice to 0.3 mg/kg of PFOS or PFOA throughout pregnancy results in different distribution pattern in the offspring brain and liver. In particular, exposure to PFOS led to four times higher accumulation of the chemical in the brains of newborn mice than PFOA. We have used a battery of behavioral tests to evaluate motor function, circadian activity, and emotion-related behavior in the exposed offspring. Exposure to PFOS resulted in decreased locomotion in a novel environment and reduced muscle strength only in male offspring. Prenatal exposure to PFOA was associated with changes in exploratory behavior in male and female offspring, as well as with increased global activity in males in their home cage. The neurobehavioral outcome of prenatal exposure to PFCs in mice is characterized by mild alterations in motor function and it appears to be sex-related.

Prenatal Perfluorooctanoic Acid Exposure in CD-1 Mice: Low-Dose Developmental Effects and Internal Dosimetry

Madisa B. Macon,*,† LaTonya R. Villanueva,‡,§ Katoria Tatum-Gibbs,*,§ Robert D. Zehr,¶ Mark J. Strynar,¶ Jason P. Stanko,† Sally S. White,† Laurence Helfant,¶ and Suzanne E. Fenton†

*Curriculum in Toxicology, University of North Carolina, School of Medicine, Chapel Hill, North Carolina 25799; †Cellular and Molecular Pathology, National Toxicology Program, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, North Carolina 27711; ‡Department of Chemistry, North Carolina Central University, Durham, North Carolina 27709; §Developmental Toxicology Branch, Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory; and ¶Methods Development and Application Branch, Human Exposure and Atmospheric Sciences Division, National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Perfluorooctanoic acid (PFOA) is an environmental contaminant that causes adverse developmental effects in laboratory animals. To investigate the low-dose effects of PFOA on offspring, timed-pregnant CD-1 mice were gavage dosed with PFOA for all or half of gestation. In the full-gestation study, mice were administered 0, 0.3, 1.0, and 3.0 mg PFOA/kg body weight (BW)/day from gestation days (GD) 1–17. In the late-gestation study, mice were administered 0, 0.01, 0.1, and 1.0 mg PFOA/kg BW/day from GD 10–17. Exposure to PFOA significantly ($p < 0.05$) increased offspring relative liver weights in all treatment groups in the full-gestation study and in the 1.0 mg PFOA/kg group in the late-gestation study. In both studies, the offspring of all PFOA-treated dams exhibited significantly stunted mammary epithelial growth as assessed by developmental scoring. At postnatal day 21, mammary glands from the 1.0 mg/kg GD 10–17 group had significantly less longitudinal epithelial growth and fewer terminal end buds compared with controls ($p < 0.05$). Evaluation of internal dosimetry in offspring revealed that PFOA concentrations remained elevated in liver and serum for up to 6 weeks and that brain concentrations were low and undetectable after 4 weeks. These data indicate that PFOA-induced effects on mammary tissue (1) occur at lower doses than effects on liver weight in CD-1 mice, an observation that may be strain specific, and (2) persist until 12 weeks of age following full-gestational exposure. Due to the low-dose sensitivity of mammary glands to PFOA in CD-1 mice, a no observable adverse effect level for mammary developmental delays was not identified in these studies.

Michigan PFOA Summary

Chemical Summary for PFOA

	Decision point	Rationale/justification
Critical study	Onishchenko N, Fischer C, Wan Ibrahim WN, Negri S, Spulber S, Cottica D, Ceccatelli S. 2011. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. Neurotox. Res. 19(3):452-61. Koskela A, Finnilä MA, Korkalainen M, Spulber S, Koponen J, Håkanss on H, Tuukkanen J, Viluksela M. 2016. Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. Toxicol. Appl. Pharmacol. 301:14-21.	The Workgroup reviewed the available evaluation and selected the ATSDR (2018) critical studies. The Workgroup concluded that the ATSDR position was defensible with respect to range and sensitivity of health endpoints identified and considered in ATSDR (2018).
Description of the critical study	Onishchenko et al.: Pregnant C57BL/6 mice were exposed to 0 or 0.3 mg PFOA/kg/day throughout pregnancy. The critical effects considered were Neurobehavioral effects (decreased number of inactive periods, altered novelty induced activity) at 5-8 weeks of age. Koskela et al.: Pregnant C57BL/6 mice were exposed to PFOA mixed with food at the dose of 0 or 0.3 mg PFOA/kg/day throughout pregnancy. Group of five offspring (female) were sacrificed at either 13 or 17 months of age. The critical effects considered were skeletal alteration such as bone morphology and bone cell differentiation in the femurs and tibias.	The Workgroup selected these developmental delays as most appropriate health endpoint as the mammary gland effects may represent a delay that may not be considered adverse. However, the mammary gland effects may be representative of endocrine effects at doses below the selected POD.
Point of Departure	The average serum concentration was estimated in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh et al. 2013) using animal species-, strain-, sex-specific parameters.	The Workgroup decided that serum-based points of departure were appropriate for PFAS.
Human equivalent dose	The time-weighted average serum concentration of 8.29 mg/L was converted to the HED using the below equation. $LOAEL_{HED}$ = (TWA serum x k_e x V_d) = 0.001163 mg/kg/day Ke = 0.000825175 (8.2×10^{-4}) based on a human serum half-life of 840 days (Bartell et al. 2010) Vd = 0.17 L/kg (Thompson et al. 2010)	The Workgroup selected the PFOA serum half-life of 840 days (2.3 years) as more relevant for exposure to the general population as this half-life corresponds to data from Bartell et al. (2010) in which 200 individuals (100 men, 100 women) were exposed by drinking PFOA-contaminated water. The Workgroup selected the volume of distribution based on human data, when available.

Michigan PFOA Summary

Uncertainty factors	A total uncertainty factor of 300: • 3 ($10^{0.5}$) for LOAEL to NOAEL • 10 for human variability • 3 ($10^{0.5}$) for animal to human variability • 1 for subchronic to chronic • 3 ($10^{0.5}$) for database deficiencies (endocrine effects)	The Workgroup discussed the use of an uncertainty factor of 3 for use of a LOAEL. They noted that a NOAEL for immune effects was similar to the LOAEL selected and that the selected LOAEL represented less severe effects. The Workgroup concluded that use of the 3 ($10^{0.5}$) would be sufficiently protective. The Workgroup added a database uncertainty factor of 3 ($10^{0.5}$) for deficiencies the database regarding endocrine effects. The Workgroup noted that the mammary gland effects may signal a concern for other low dose endocrine effects.
Toxicity value	3.9 ng/kg/day (3.9 x 10^{-6} mg/kg/day) which corresponds to a serum concentration of 0.028 mg/L Serum levels used in development of these toxicity levels are not meant to indicate a level where health effects are likely. These serum levels are calculated to be at a point where no or minimal risk exists for people drinking water with a certain PFAS.	Human equivalent dose or serum level divided by the total uncertainty factors = toxicity value
Exposure parameters for drinking water HBVs	Breast-fed infant, which is also protective of a formula-fed infant Placental transfer of 87% (MDH 2017) Breastmilk transfer of 5.2% (MDH 2017) Human Serum half-life of 840 days (Bartell et al. 2010) Volume of distribution of 0.17 L/kg (Thompson et al. [2010]) 95th percentile drinking water intake, consumers only, from birth to more than 21 years old (Goeden et al. [2019]) Upper percentile (mean plus two standard deviations) breast milk intake rate (Goeden et al. [2019]) Time-weighted average water ingestion rate from birth to 30-35 years of age (to calculate maternal serum concentration at delivery) (Goeden et al. [2019]) Relative Source Contribution of 50% (0.5) Based on NHANES 95th percentiles for 3-11 (2013-2014) and over 12 years old (2015-2016) participants (CDC 2019)	The Workgroup discussed the Goeden et al. (2019) model which considered full life stage exposure, from fetal exposure, to infant exposure through breastfeeding, and into adulthood. While the model was also developed for a formula-fed infant, the breastfed infant scenario is protective of a formula-fed infant. The Workgroup selected this model for developing drinking water HBVs when the needed inputs were available.
Drinking water HBV	8 ng/L (ppt)	Numeric HBV derived and justified using the above information

Massachusetts Study Selection

The differences between the USEPA RfD and these other toxicity values for PFOA and PFOS, as well as the additional values derived for PFNA and PFHxS, prompted MassDEP to re-evaluate its toxicity and associated drinking water guidance values for these and closely related compounds. As part of MassDEP efforts to address PFAS compounds, MassDEP has reviewed numerous published toxicological assessments and key primary literature publications. These include the USEPA Health Effects Support and Drinking Water Health Advisory (HA) documents for PFOA and PFOS (USEPA 2016a,c,b,d); the ATSDR draft Toxicological Profile for Perfluoroalkyls (ATSDR 2018a); the National Toxicology Program (NTP) Monograph, Immunotoxicity Associated with Exposure to PFOA or PFOS (NTP 2016); the New Jersey Drinking Water Quality Institute (NJDWQI) Maximum Contaminant Level (MCL)

This re-evaluation does not seek to replicate the extensive work already completed and detailed in the noted assessments but rather focuses on key evidence and publications associating

Massachusetts Reference Dose Selection

2.1 Summary of USEPA RfDs for PFOA and PFOS

The USEPA (2016a,b) RfDs for PFOA and PFOS (2×10^{-5} mg/kg-day) are based on multiple studies and endpoints. In deriving these values, USEPA extensively reviewed the available human and animal toxicity studies on PFOA and PFOS and selected results from several studies representing various effects and life stages as points of departure (PODs) to derive candidate RfDs for PFOA and PFOS (Tables 1 and 2, respectively) (USEPA 2016 a,b,c,d). USEPA selected the candidate studies and PODs based on their NOAELs/LOAELs, use of control groups, use of two or more doses, and the availability of measured or modeled serum levels. For both PFOA and PFOS, eleven of the twelve candidate RfDs derived by USEPA were within the range of $2 - 5 \times 10^{-5}$ mg/kg-day. These included values derived for several endpoints. The POD and associated RfD selected by USEPA (2016a,b) for both compounds was the lowest and most frequent of the candidate RfD values derived, 2×10^{-5} mg/kg-day[1].

Massachusetts Study Selection

Table 1. USEPA (2016a) Candidate RfDs Derived from Modeled Animal Average Serum Values of PFOA

Study	Endpoint	Dosing duration (days)	LOAEL (Av serum mg/L) [a]	UFs (total and components)	Candidate RfD (mg/kg-day)
Lau et al. (2006) CD1 mice N not specified	**Pup ossification (m, f) accelerated puberty (m)**	**17** (GD 1–17)	**38.0**	**300 UF_H = 10 UF_A = 3 UF_L = 10**	**2 x 10^{-5} (USEPA RfD)**
DeWitt et al. (2008) C57BL/6N mice N = 8	↓ IgM response to SRBC	15	61.9 [b]	300 UF_H = 10 UF_A = 3 UF_S = 10	2 x 10^{-5}
Palazzolo (1993); Perkins et al. (2004) ChR-CD rat (m) N = 45-55/dose group	↑ Liver weight ↑ Liver necrosis	91	77.4 [c]	30 UF_H = 10 UF_A = 3	1.5 x 10^{-4}
Wolf et al. (2007) CD-1 mice N = 28-48/dose group	↓ Pup body weight	17 (GD 1–17)	77.9	300 UF_H = 10 UF_A = 3 UF_L = 10	4 x 10^{-5}
Wolf et al. (2007) CD-1 mice N = 14	↓ Pup body weight	11 (GD 7–17)	87.9	300 UF_H = 10 UF_A = 3 UF_L = 10	4 x 10^{-5}
Butenhoff et al. (2004) Sprague-Dawley rat N = 30/sex/group	↓ Rat relative body weight/↑ relative kidney weight and ↑ kidney:brain weight ratio in F0 and F1 at sacrifice	84	45.9	300 UF_H = 10 UF_A = 3 UF_L = 10	2 x 10^{-5}

[a]

Massachusetts Reference Dose Discussion

The MassDEP RfD for the subclass is based on that for PFOA and PFOS. The bases of MassDEP's updated RfDs for these compounds was previously described. In summary, MassDEP relied on the same POD and HED calculations used by USEPA with inclusion of an additional UF to account for data indicating effects at lower dose levels, resulting in a RfD of 5.3 x 10^{-6} (rounded to 5 x 10^{-6} mg/kg/day) for PFOA[23] and of 5.1 x 10^{-6} mg/kg/day (rounded to 5 x 10^{-6} mg/kg/day) for PFOS.[24] The RfDs rounded to one significant figure are the same (5 x 10^{-6} mg/kg/day) and this value was adopted for the PFAS subgroup addressed by MassDEP.

Massachusetts Reference Dose Discussion

2.3.1 *PFOA*

Several studies have demonstrated various effects at dose levels below that selected as a POD by the USEPA (2016a). These include neurobehavioral, skeletal, and mammary gland development (Table 3) and hepatic toxicity endpoints (Table 4). MassDEP has concluded that these studies, taken together, provide compelling evidence that effects at exposures below the POD selected by USEPA in its RfD derivation for PFOA are likely. However, as discussed below, because of certain questions regarding the appropriate use of the noted data in selecting an alternative POD, MassDEP has instead elected to account for this data through the use of a database uncertainty factor.

Massachusetts Reference Dose Discussion

Table 7. Human Equivalent Doses (HEDs) and RfDs Derived from the Modeled Animal Average Serum Values of PFOA by Various Agencies

Agency	Study	Dosing duration (days)	LOAEL (Av serum mg/L)	HED (ug/kg-day)	UFs (total and components)	RfD (mg/kg-day)
USEPA (2016a)	Lau et al. (2006) CD-1 mice Decreased pup ossification and accelerated male puberty	17	38 [a]	5.3	300 UF_H = 10 UF_A = 3 UF_L = 10	2 x 10^{-5}
ATSDR (2018a)	Onishchenko et al. (2011) C57BL/6 mice Neurodevelopment; Koskela et al. (2016) Skeletal development	17	8.29 [b]	0.821	300 UF_H = 10 UF_A = 3 UF_L = 10	3 x 10-6
MDH (2018a)	Lau et al. (2006) CD-1 mice Decreased pup ossification and accelerated male puberty	17	38 [a]	5.3	300 UF_H = 10 UF_A = 3 UF_L = 3 mild effect **UF_D = 3 no 2-generation**	2 x 10^{-5} (1.8 x 10^{-5})
NJDWQI (2017)	Loveless et al. (2006) CRL:CDs mice Increased relative liver weight	14	13 [c]	0.61 [d]	300 UF_H = 10 UF_A = 3 **UF_D = 10 developmental mammary**	2 x 10^{-6}
NHDES (2019b)	Loveless et al. (2006) CRL:CDs mice Increased relative liver weight	14	13 [c]	0.61 [d]	100 UF_H = 10 UF_A = 3 **UF_D = 3 developmental mammary**	6 x 10^{-6} (6.1 x 10^{-6})

Massachusetts Reference Dose Discussion

MassDEP, Office of Research and Standards

Agency	Study	Dosing duration (days)	LOAEL (Av serum mg/L)	HED (ug/kg-day)	UFs (total and components)	RfD (mg/kg-day)
MISAW (2019)	Onishchenko et al. (2011) C57BL/6 mice Neurodevelopment; Koskela et al. (2016) Skeletal development	17	8.29 [b]	1.163	300 $UF_H = 10$ $UF_A = 3$ $UF_L = 3$ **$UF_D = 3$ endocrine effects**	4×10^{-6} (3.9×10^{-6})
NYDOH (2019)	Macon et al. (2011) CD-1 mice Increased pup relative liver weight on PND 7 male and female pups	17	4.98 [e]	0.15 [d]	100 $UF_H = 10$ $UF_A = 3$ **$UF_D = 3$**	1.5×10^{-6}
WIDHS (2019)	Lau et al. (2006) CD-1 mice Decreased pup ossification and accelerated male puberty	17	[f]	0.54 (HED_{50})	300 $UF_H = 10$ [g] $UF_A = 3$ $UF_L = 10$	2×10^{-6}
MassDEP ORS	Lau et al. (2006) CD-1 mice Decreased pup ossification and accelerated male puberty	17	38 [a]	5.3	1000 $UF_H = 10$ $UF_A = 3$ $UF_L = 10$ **$UF_D = 3$ developmental mammary and liver**	5×10^{-6} (5.3×10^{-6})

[a] Average serum concentration modeled by USEPA (2016a) using Wambaugh et al. (2013) to estimate an AUC

Massachusetts Drinking Water Standard

The derivation of the MassDEP drinking water value based on this RfD is described below:

$$\text{Drinking water value} = \frac{\text{RfD} \times \text{RSC}}{\text{Water consumption rate per kg body weight}}$$

Where:

RfD	$= 5 \times 10^{-6}$ mg/kg-day
Water consumption rate for lactating woman	= 0.054 L/kg-day
Relative Source Contribution Factor (RSC)	= 0.2

$$\text{Drinking Water Value} = \frac{5 \times 10^{-6} \text{ mg/kg-day} \times 0.2}{0.054 \text{ L/kg-day}}$$

$$= 0.0000185 \text{ mg/L}$$

= 0.00002 mg/L or 20 ng/L (20 ppt), rounded to one significant figure

When these six compounds occur alone, together, or in any combination, the sum of their concentrations should be compared to 0.00002 mg/L.

New Hampshire Principal Study and Point of Departure

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.

New Hampshire – Cancer Discussion

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.

New Hampshire Point of Departure

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

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

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).

New Hampshire Uncertainty Factors

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

New Hampshire

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,

New Hampshire

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

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

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.

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

New Hampshire

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.

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

New Hampshire Reference Dose

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.

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

New Hampshire Reference Dose

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.

New Hampshire Reference Dose

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).

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

New Jersey

Continued exposure to even low drinking water concentrations results in substantially increased serum PFOA levels. Based on the clearance factor, each 10 ng/L in drinking water is predicted to increase serum PFOA by 1.1 ng/ml with an average water consumption rate, and 2.0 ng/ml with an upper percentile water consumption rate. These increases in serum PFOA from drinking water can be compared to the most recent NHANES geometric mean, 2.08 ng/ml, and 95th percentile, 5.68 ng/ml, serum PFOA concentrations. Increases in serum PFOA levels predicted from average and upper percentile drinking water consumption at various drinking water PFOA concentrations are shown in Figure E-1.

New Jersey

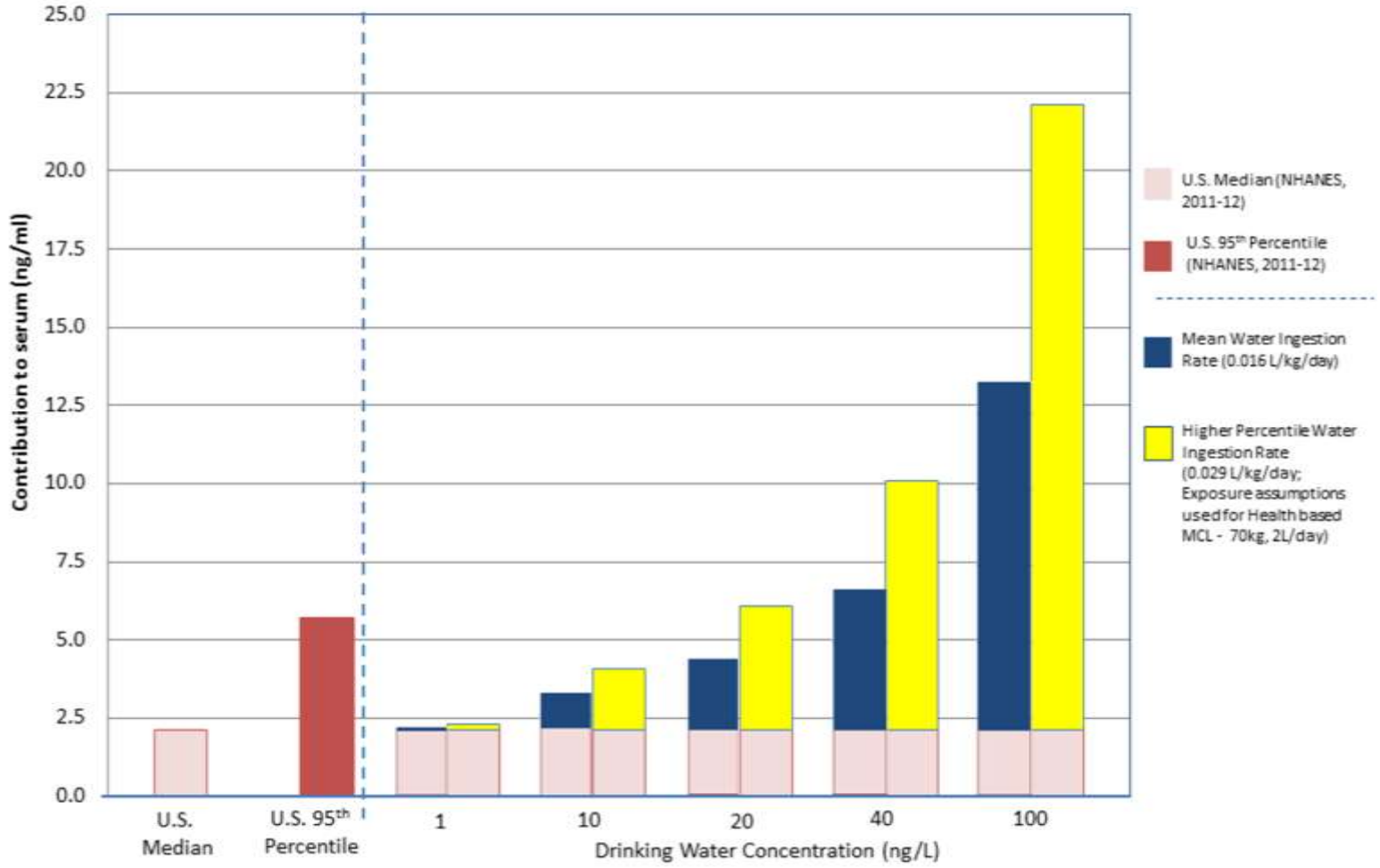


Figure E-1. Increases in serum PFOA concentrations predicted from mean and upper percentile consumption of drinking water with various concentrations of PFOA, as compared to U.S median and 95th percentile serum PFOA levels (NHANES, 2011-12).

New Jersey Approach to Reference Dose

Health-based MCL based on non-carcinogenic effects

Delayed mammary gland development and increased relative liver weight were identified as the most sensitive non-carcinogenic endpoints with data appropriate for dose-response modeling, and it was concluded that these endpoints are relevant to humans for the purposes of risk assessment. Benchmark dose (BMD) modeling of serum PFOA data from toxicological studies was performed to determine the BMDLs (lower 95% confidence limit on the doses corresponding to a minimal response) for the serum concentrations that are used as the points of departure (PODs) for these endpoints. Only studies that provide serum PFOA data were considered for dose-response modeling for these effects, since measured serum levels are associated with less uncertainty than serum level estimates from pharmacokinetic modeling or interspecies extrapolations based on half-life differences.

New Jersey Uncertainty Factors (Mammary gland development)

A total UF of 30, including UFs of 10 for intra-human variability and 3 for animal-to-human toxicodynamic differences, was applied to the serum level BMDL for decreased number of terminal end buds, 22.9 ng/ml, to derive a Target Human Serum Level of 0.8 ng/ml. The typical UF of 3 for toxicokinetic variability between species is not included because the risk assessment is based on comparison of internal dose (serum levels) rather than administered dose. The Target Human Serum Level is analogous to a RfD in terms of internal, rather than administered, dose. This Target Human Serum Level for delayed mammary gland development of 0.8 ng/ml is below the median serum PFOA level in the U.S. general population (2.1 ng/ml). The clearance factor mentioned above, 1.4×10^{-4} L/kg/day, was applied to the Target Human Serum Level, 0.8 ng/ml, to calculate an RfD of 0.11 ng/kg/day.

New Jersey Approach to Reference Dose

Health-based MCL based on non-carcinogenic effects

Delayed mammary gland development and increased relative liver weight were identified as the most sensitive non-carcinogenic endpoints with data appropriate for dose-response modeling, and it was concluded that these endpoints are relevant to humans for the purposes of risk assessment. Benchmark dose (BMD) modeling of serum PFOA data from toxicological studies was performed to determine the BMDLs (lower 95% confidence limit on the doses corresponding to a minimal response) for the serum concentrations that are used as the points of departure (PODs) for these endpoints. Only studies that provide serum PFOA data were considered for dose-response modeling for these effects, since measured serum levels are associated with less uncertainty than serum level estimates from pharmacokinetic modeling or interspecies extrapolations based on half-life differences.

New Jersey Uncertainty Factors (Increased Liver Weight)

A total UF of 300 was applied to the serum level BMDL of 4350 ng/ml to derive a Target Human Serum Level of 14.5 ng/ml. This UF includes UFs of 10 for intra-human variability, 3 for animal-to-human toxicodynamic differences, and 10 to protect more sensitive toxicological effects. These more sensitive effects, including delayed mammary gland development and hepatic toxicity after developmental exposures, occurred at doses 100-fold lower than the Lowest Observed Adverse Effect Level (LOAEL) for increased liver weight. Although the study duration was only 14 days and the Health-based MCL is intended to protect for chronic exposure, a UF for less-than-chronic duration of exposure was not applied because increased liver weight does not appear to increase in magnitude when exposures continue beyond two weeks. The clearance factor mentioned above, 1.4×10^{-4} L/kg/day, was applied to the Target Human Serum Level, 14.5 ng/ml, to calculate an RfD of 2 ng/kg/day.

New Jersey Relative Source Contribution

There are no New Jersey-specific biomonitoring data for PFOA, and the more frequent occurrence in NJ PWS suggests that New Jersey residents may also have higher exposures from non-drinking sources, such as contaminated soils, house dust, or other environmental media, than the U.S. general population. Additionally, the default RSC of 20%, while not explicitly intended for this purpose, also partially accounts for the greater exposures to infants who are breast-fed or consume formula prepared with contaminated drinking water, as compared to older individuals. These higher exposures during infancy must be considered because short term exposures to infants are relevant to the effects of concern (delayed mammary gland development and increased relative liver weight). Therefore, the default RSC of 20% was used to develop the Health-based MCL.

Vermont Selection of End Point

The concentration of PFOA and PFOS combined is not to exceed the DWHA based on the following recommendation presented in the May 2016 U.S. Environmental Protection Agency's (EPA) Drinking Water Health Advisory for PFOA: "The effects that serve as the basis for the RfDs [oral reference dose] for both PFOA and PFOS are developmental endpoints (reduced ossification and accelerated puberty in males for PFOA and decreased pup birth weight for PFOS). Because the RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical, where these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the HA [health advisory]."[1]

Vermont Selection of End Point

Details of the derivation of the Drinking Water Health Advisory of 20 ppt for PFOA and PFOS combined follow.

Drinking Water Health Advisory - Noncancer

1. The general equation used to derive a noncancer-based Drinking Water Health Advisory:

   $DWHA = (HQ)(RfD_o)(1/BW_AIR)(CF)(RSC)$

   DWHA = Drinking Water Health Advisory
   HQ= Hazard Quotient
   RfD_o= chronic oral reference dose
   BW_AIR= Body Weight adjusted Water Intake Rate
   CF= Units Conversion Factor
   RSC= Relative Source Contribution

Vermont Exposure Assumptions

Exposure Assumptions, Parameter Values and Descriptions

HQ = 1

Target Hazard Quotient employed in the development of Department of Health Drinking Water Guidance Values

RfD_o = $2x10^{-5}$ mg/kgBW-d

Oral reference dose provided in EPA's 2016 Health Effects Support Document for PFOA[2] and PFOS[3]

BW_AIR = 0.175 L/kgBW-d

The 2016 EPA Drinking Water Health Advisories for PFOA[1] and PFOS[4] state that "the developing fetus and newborn are particularly sensitive to PFOA- and PFOS-induced toxicity." EPA has recommended that fine age groupings be used in the assessment of potential exposure to children[5]. A series of ten ranges between birth and 21 years of age is recommended for consideration as appropriate. The 95th percentile Body Weight Adjusted Water Intake Rate for the first year of life based on combined direct and indirect water intake from community water supplies for consumers only is 0.175 L/kgBW-d[6,7].

CF= 1000 µg/mg

Unit conversion from milligrams to micrograms

Vermont Relative Source Contribution

RSC = 0.2 (20%)

Consistent with EPA guidance[8,9], an RSC is incorporated in the development of DWHAs that are based upon a threshold type, primarily noncarcinogenic, health effect. The RSC represents the portion of an individual's total daily exposure to a specific chemical that is attributed to or allocated to drinking water. An RSC of 20% is incorporated to account for exposure to PFOA and PFOS from other sources. This follows EPA's recommendation to use an RSC of 20% when quantitative data on other sources of exposure are not available. The 2016 PFOA Health Advisory states "In cases where environmental or exposure data are lacking, the Exposure Decision Tree approach results in a recommended RSC of 20%. This 20% RSC value may be replaced where sufficient data are available to develop a scientifically defensible alternative value."[1]

New York PFOA MCL

Watch Video

Discussion

- Old Dominion University to provide research
  - Topics
    - Relative source contribution, water ingestion rate, EPA RSC flowchart, contribution from non drinking water
    - Toxicokinetics – DAF, adsorption, volume of distribution, serum, ½ lives between compounds, which ½ life is used – male or female
    - Animal models – rats vs. mice vs etc…
    - NHANES studies
    - History of use of uncertainty factors and modifying factors (database)
    - Are vulnerable subpopulations identified in the report (particularly ATSDR)
    - ATSDR did assign MRL to PFOA – no chronic data
    - PFAS affect on immune response – without more people getting sick – is that an adverse affect
    - What makes an adverse effect
    - No effect vs. no adverse effect
    - Additive affect, combining compounds, regulate as a class, etc…

Public Comments

Next Meeting