THE ENDOCRINE DISRUPTION EXCHANGE
Partners in Science

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Re: Setting Public Drinking Water and Groundwater Standards for PFOA, PFOS, PFNA, & PFHxS (Env-Dw 700-800; Env-Or 603.03)

On behalf of The Endocrine Disruption Exchange (TEDX), we appreciate this opportunity to submit comments in support of NHDES Env-Dw 700-800 and Env-OR 603.03 regarding the setting of public drinking water and groundwater standards for PFOA, PFOS, PFNA, and PFHxS. TEDX is a nonprofit research institute that advocates for and practices the objective and transparent translation of basic research on endocrine disrupting chemicals.

Given that the science on per- and polyfluoroalkyl substances (PFAS) is rapidly growing, and that there is widespread exposure to these compounds in the state of New Hampshire, it is imperative that NHDES act swiftly to set maximum contaminant levels (MCLs) and ambient groundwater quality standards (AGQS) for drinking and groundwater that will protect the safety of New Hampshire citizens, especially those who are most vulnerable to the harmful health effects associated with PFAS and those at highest risk due to heightened exposure. Unfortunately, the MCLs and AGQS currently proposed by NHDES are not protective enough for the citizens of New Hampshire, particularly infants and children and those who have potentially been exposed to complex mixtures of these persistent and bioaccumulative chemicals for several decades.

We have thoroughly evaluated the Summary Report document, which outlines NHDES's justification for the derivation of each proposed MCL and AGQS (henceforth referred to as MCLs) (NHDES 2019b). Overall, we feel that assumptions and professional judgements made by NHDES were consistently less protective of public health. Our comments highlight these decisions, and offer reasonable and scientifically justifiable alternatives, several of which have been proposed or used by other state level agencies in the US. We have also evaluated new literature that has come available since the announcement of the proposed values by NHDES, including transgenerational toxicokinetic models of exposure for PFOA, PFOS, and PFHxS. We have used this new information to propose MCLs that are scientifically justifiable and more protective of human health.

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Based on our analysis of the Summary Report and incorporation of new exposure models, we suggest the following MCLs be adopted by NHDES:

- **PFOA: <1 ppt (and no more than 3 ppt)** based on application of the new transgenerational toxicokinetic model for PFOA exposure proposed by MN Department of Health (MN DH), and either selecting the effects on the mammary gland as the critical endpoint or applying additional uncertainty factors to account for these effects (See Appendix 1).
- **PFOS: 13 ppt** based on application of the new transgenerational toxicokinetic model for PFOS exposure proposed by MN DH and selecting the immunotoxic effects as the critical endpoint (See Appendix 2).
- **PFNA: 1 ppt** based on the application of exposure estimates specific for infants, the application of additional uncertainty factors to account for the short duration of exposure in the selected critical study, and use of a more representative half-life (See Appendix 3).
- **PFHxS: 30 ppt** based on application of the new transgenerational toxicokinetic model for PFOS exposure proposed by MN DH and a more representative value for the volume of distribution (See Appendix 4).

Background

With models and formulas available for deriving MCLs, it would seem that arriving at safe drinking water levels would be straightforward, and that one could rely solely on the available science. Yet, a deeper understanding of the models and formulas for deriving MCLs reveals numerous places where professional judgment must be used and where assumptions are likely to be made (Cordner et al. 2019). Unfortunately, at nearly every opportunity, NHDES has made assumptions and used expert professional judgement that is not protective of sensitive populations, particularly fetuses, infants, young children, and the chronically exposed. This becomes abundantly clear when the MCL values proposed by NHDES are shown in comparison to those proposed by other state agencies, in particular, those proposed by NJ (Figure 1). **Importantly, the differences between the values proposed by NH and NJ are not due to differential availability of scientific studies. Instead, the differences arise due to the assumptions and professional judgements exercised by the various state agencies.**

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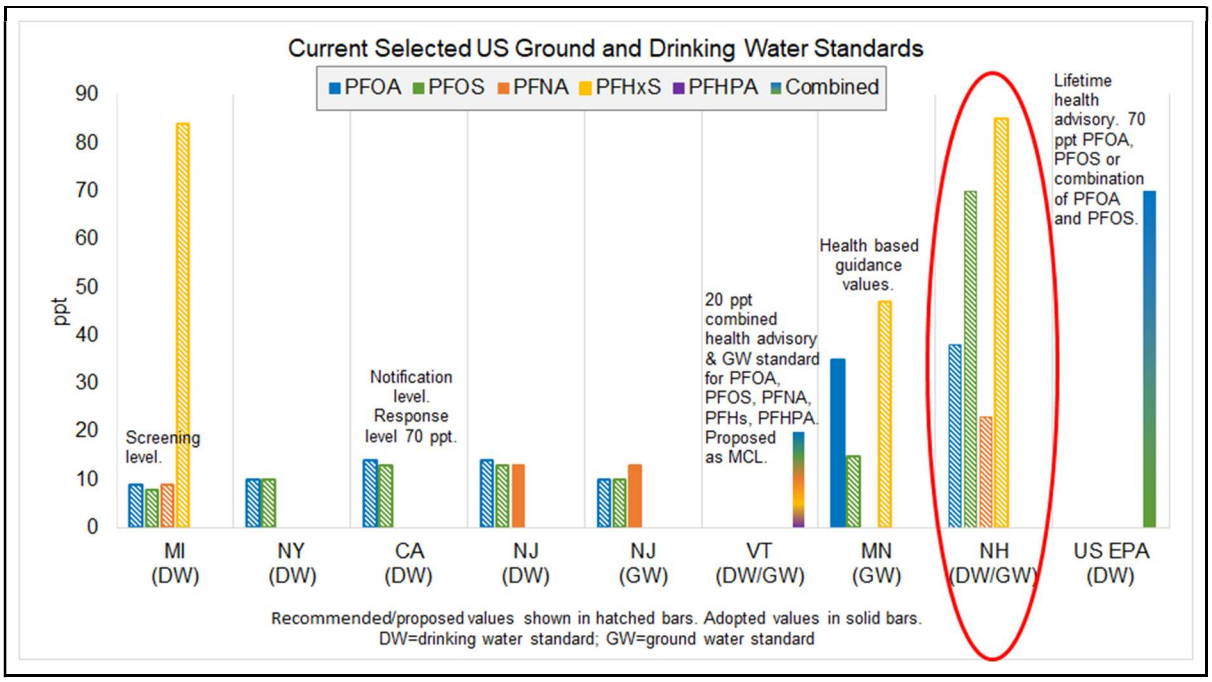
Figure 1. Selected US Ground and Drinking Water Standards for Five PFAS



In our comments, we highlight the steps in the MCL derivation process where the assumptions and professional judgements used by NHDES were not protective enough. Specifically, these are:

- **selection of exposure estimates (PFOA, PFOS, PFNA, PFHxS),**
- **choice of critical study selection (PFOA, PFOS),**
- **choice of uncertainty factors (UF) (PFOA, PFOS, PFNA),**
- **selection of half-life value (PFNA),**
- **and calculation of the volume of distribution (PFHxS).**

Our comments below show how each of the professional judgements made by NHDES impact the final MCL number.

NHDES did not use protective exposure assumptions.
For the calculation of each MCL, NHDES used exposure assumptions for water ingestion based on lactating women. NHDES stated:

> *To afford additional protection for chronic exposure, daily water intake was assumed to be that of the 95th percentile for lactating women, which is the highest water in-take rate for adults (i.e., for a 175 lb. person, this would equal about 4.4 liters of water consumed each day. By using this rate of water intake to*

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calculate the MCLs, the levels are expected to be safe for pregnant mothers and their fetuses, lactating mothers and their infants, and all children, adolescents, and adults). This high intake rate was assumed "through life" as a protective measure. (NHDES 2019b)

We appreciate the effort of NHDES to protect lactating women. However, to our knowledge, there is no empirical evidence that using the rate of water intake for lactating women is protective for infants, children, adolescents, and adults. No citation to support this statement was provided by NHDES. On the contrary, the US EPA estimates that infants consume 5 times more water on a per body weight basis than lactating women (0.137 L/kg-day vs 0.026 L/kg-day) (US EPA 2011). In fact, it is not until ages 6-11 that water intake rates approximate adult rates on a per body weight basis (Goeden 2018).

To correct this oversight, **NHDES must use appropriate exposure estimates based on infants.** Two states, VT and MN, have already incorporated exposure estimates for infants, thereby paving the way for NHDES to do so as well. VT has used 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 (US EPA 2011; Vermont 2018). This value is 0.175 L/kg-day. **Incorporating this exposure value into the MCL calculations currently proposed by NHDES would reduce the final MCL of each chemical by a factor of more than 3-fold. Proposed MCLs would then become 12, 23, 7, and 27 ppt for PFOA, PFOS, PFNA, and PFHxS, respectively (Table 1).**

Table 1. Impact of incorporating infant specific exposure rates on NHDES proposed MCLs

	PFOA (ppt)	PFOS (ppt)	PFNA (ppt)	PFHxS (ppt)
MCLs currently proposed by NHDES	38	70	23	85
MCLs if infant specific exposure rates used	12	23	7	27
Full calculations can be found in Appendices 1-4.				

MN DH has taken a different approach to incorporating infant exposures, using chemical specific toxicokinetic parameters including placental and breast milk transfer (Goeden et al. 2019). Importantly, this new model prepared by MN DH takes into account that babies are born with a transgenerational body burden from placental

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transfer based on maternal accumulation, and that infants may also experience subsequently higher exposures, due to higher body weight adjusted water intake rates and/or the partitioning of PFAS in breast milk (Goeden et al. 2019). The model has been available since August 2018, when it was adopted as rule by MN DH for PFOA (MN DH 2018). Importantly, the model has been peer-reviewed and was published in the Journal of Exposure Science & Environmental Epidemiology on January 10, 2019 (Goeden et al. 2019) . NHDES stated on February 21, 2019, that it may incorporate use of this model for derivation of MCLs (NHDES 2019a), but has provided no further information to what the new levels might be, beyond stating that "health-based drinking water or groundwater standards for PFOA and PFOS would potentially be lowered significantly below the initial proposal figures of 38 parts per trillion (ppt) and 70 ppt, respectively." It should be noted that on April 3, 2019, MN DH released for web publication the chemical-specific model parameters and results for PFOS and PFHxS (MN DH 2019a; b). MI Department of Health and Human Services (MI-DHHS) has already incorporated the use of the MN DH model for PFOA, PFOS and PFHxS, and has also extended its use to include values for PFNA (MI-DHHS 2019).

MN DH has kindly and freely made available the transgenerational toxicokinetic model in Microsoft Excel format, which allows other users to input chemical-specific parameters and/or account for the use of different critical effects and points of departure (Goeden et al. 2019). Using the MN DH transgenerational toxicokinetic model and associated Excel file, users input the target serum concentration for the reference dose (RfD) and chemical-specific parameters including: chemical half-life, placental transfer, breast milk transfer, and volume of distribution (V_d) then iteratively input drinking water concentrations so that the modeled serum concentration does not peak above a 50% relative source contribution (RSC) ceiling and is maintained below a lifetime steady state RSC of 20%. For all chemicals, two exposure scenarios were examined: an infant fed formula reconstituted with contaminated water or an infant exclusively breast-fed for 12 months, both followed by drinking contaminated water through life. **Incorporating the MN DH transgenerational toxicokinetic model into the NHDES calculations, while holding constant the other chemical specific parameters (including the target human dose, half-life, and V_d) that have already been proposed by NHDES would result in MCLs of 10, 38, 7, and 44 ppt for PFOA, PFOS, PFNA, and PFHxS, respectively (Table 2).**

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Table 2. Impact of incorporating MN DH transgenerational toxicokentic modeled exposure rates on NHDES proposed MCLs

	PFOA (ppt)	PFOS (ppt)	PFNA (ppt)	PFHxS (ppt)
MCLs currently proposed by NHDES	38	70	23	85
MCLs if modeled on formula fed infants	26	40	12*	44
MCLs if modeled on breast fed infants	10	38	7*	49
*MN DH has not yet posted a transgenerational toxicokinetic model for PFNA, but MI-DHHS has applied the model using a placental transfer value for PFNA of 0.69 and breast milk transfer value of 0.032 (MI-DHHS 2019). Model parameters and associated plots can be found in Appendices 5-8.				

NHDES did not choose the correct critical study on which to base MCLs for PFOA and PFOS.

The sequence of steps taken to derive MCLs is outlined in the NHDES Summary Report (NHDES 2019b) where it is noted that the first step is to **identify "the most sensitive adverse effect that is thought to be relevant to humans."** NHDES did not choose the most sensitive adverse health effects for PFOA or PFOS.

In the summary report, NHDES noted that the mechanism of action is not currently known for PFOA associated disruption of mammary gland development and PFOS associated immunotoxicity. For example, NHDES says "this is a major challenge for scientifically demonstrating causality" (NHDES 2019b), suggested that this is a reason that these endpoints should not be used as the basis for deriving MCLs. Yet, a known mechanism of action was not stated as a requirement for the selection of the critical effect. In fact, NHDES did not present a mechanism of action for the critical effect chosen for PFOS (developmental delays).

NHDES should base the PFOA MCL on disrupted mammary gland development.

The effects of PFOA on mammary gland are well-studied. However, in the Summary Report, NHDES has called into question the mechanism of action by which PFOA impacts mammary gland development and the functional consequences of altered mammary gland development (NHDES 2019b). It has been pointed out, however, that the mechanism of action and functional consequences of other health endpoints chosen as critical endpoints by ATSDR and US EPA is also lacking (Roberts 2018).

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The discussion of the mechanism of action for PFOA effects on mammary gland in the Summary Report (NHDES 2019b) were very focused on a mechanism of action involving peroxisome proliferator-activated receptor (PPAR)-α, leaving other potential mechanisms largely unexplored and undiscussed. For example, NHDES states that delayed mammary gland development "is possibly due to PPAR activation in mice. PPAR-associated binding proteins have been implicated in mammary duct development in mice models, as their inactivation results in delayed mammary gland development." Yet, inactivation of other nuclear receptors, for example estrogen receptor alpha (ERα) and progesterone receptor results in the similar effects and were not discussed at all by NHDES (Humphreys et al. 1997; Walker and Korach 2004).

Further, NHDES incorrectly assumed and did not support their argument that a PPARα mechanism of PFOA disruption of mammary gland development identified in rodents is not relevant to humans. This conclusion seems to be based largely on ongoing discussion of the relevance of a PPARα mediated effect of PFOA effects in the liver, which would not necessarily apply to the mammary gland. On the contrary, PPARα is expressed in human breast tissue, is upregulated in breast cancer, and therefore a PPARα mediated pathway of PFOA disruption is potentially relevant in humans (Chandran et al. 2016; Suchanek et al. 2002).

Measuring a functional consequence of altered mammary gland development is difficult in rodent models. One metric that has been suggested for use is to evaluate pup body weight and to look for potential deficits in weight gain, as this may signal difficulties in lactation. One study has reported reduced pup body weight in animals that were gestationally exposed to PFOA (White et al. 2007). White et al. tried to tease out if the reduced pup body weight was a direct result of the pup being exposed to PFOA or if was an effect mediated through the exposed mother. To this end, the mammary glands from lactating mothers exposed to PFOA were underdeveloped and displayed delayed development compared to vehicle treated control animals (Whiteet al. 2007). Importantly, the delays in mammary gland were apparent prior to the initiation of suckling, which supports the suggestion that PFOA altered mammary gland differentiation had direct functional consequences on lactation (White et al. 2007).

While it seems that pup body weight could be a good proxy assessment, the reality is that it is not a very sensitive endpoint for measuring deficits in lactation. What is not captured in measurements of pup body weight are potential compensatory mechanisms, including the number of nursing events, duration of nursing events, volume of milk output, and timing to peak milk output. White and colleagues attempted to assess some of these mechanisms in a follow-up study (White et al. 2011). The authors noted trends in longer time to suckling and reduced milk volume, though variability in these findings rendered them not statistically significant (White et al. 2011). Importantly, in humans, changes in any or all of these potential compensatory mechanism could impact a woman's ability to successfully breastfeed. In fact, three

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human studies report that maternal PFOA exposure is associated with decreased duration of breastfeeding (Fei et al. 2010; Romano et al. 2016; Timmermann et al. 2017).

We agree with NJ Department of Environmental Protection (NJDEP) who stated in public comments submitted to NHDES that **changes in mammary gland should be considered adverse and used for risk assessment**. NJDEP stated:

> *[Delayed mammary gland development is considered to be adverse because structural changes in the mammary gland persisted until adulthood, and there is no reason to discount its human relevance. Furthermore, three human studies report that PFOA is associated with decreased duration of breastfeeding.* (NJDEP 2018)

NHDES should calculate the PFOA MCL using the RfD calculated by NJ Drinking Water Quality Institute (NJDWQI) based on changes in the developing mammary gland (NJDWQI 2017). To arrive at this value, NJDWQI applied benchmark dose modeling to determine the internal serum level of PFOA in animals from Macon et al. 2011 that displayed changes in mammary gland development and terminal end bud numbers following developmental PFOA exposure (Maconet al. 2011). NJDWQI used the lowest significant benchmark dose (lower confidence limit) (BMDL), for decreased number of terminal end buds, of 22.9 ng/ml in serum, as the point of departure (POD) for RfD development. The POD should then be divided by an UF of 30 (10 for human variation and 3 for animal-to-human extrapolation) to reach a target serum human level of 800 ng/L. **Incorporating this target serum human level derived by NJDWQI for mammary gland effects into the NHDES MCL calculations results in a MCL for PFOA of 0.67 ppt (Table 3).**

<u>NH DES should base the PFOS MCL on immunotoxicity endpoints.</u> Immunotoxicity is currently the most sensitive health endpoint for PFOS exposure and is relevant to human health, the two criteria NHDES stated were used to identify the critical effect (NHDES 2019b). In 2016 the National Toxicology Program (NTP) concluded that PFOS is “presumed to be an immune hazard to humans based on a high level of evidence that PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans” (NTP 2016). NTP reported that PFOS exposure in humans is associated with suppression of the anti-vaccine antibody response (NTP 2016). **In the Summary Report NHDES does not explicitly state why immunotoxicity was not considered the critical effect for the basis of the PFOS calculations (NHDES 2019b)**. In fact, NHDES downplays the reported association of PFOS in epidemiological studies by citing a 2016 report by Chang et al., stating:

> *Epidemiology studies have identified varying associations for PFOS with immunomodulation (reviewed NTP 2016; ATSDR 2018), although these*

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associations have been disputed for a variety of criteria (Chang et al. 2016). (NHDES 2019b)

It is critical to note that the assessment of immunotoxicological endpoints conducted by NTP was performed in a transparent manner using gold-standard systematic review methods and included a formal analysis of the risks of bias for the studies that were reviewed. In contrast, the report prepared by Chang et al. was funded by 3M, written by authors who have declared numerous conflicts of interest (having been former employees of 3M), it did not follow standard systematic review methods, and did not analyze the risks of bias of included studies. **As such, the review by Chang et al. cannot be used to discount the conclusions reached by NTP and ultimately the relevance of PFOS associated immunotoxicity.** For more details on how industry sponsorship of toxicological research and risk assessment has influenced ongoing discussions on PFAS see (Cordner et al. 2019).

NJDWQI chose the 2009 study by Dong et al. reporting decreased plaque forming immune response as the critical study on which to base their calculations (Dong et al. 2009). Dong et al. 2009 was one of four immunological studies evaluated by ATSDR, two of which had no adverse effect levels (NOAELs) lower than that reached by Dong et al. 2009 (ATSDR 2018). The data from Dong et al. 2009 was not amenable to BMD modeling and so the NOAEL of 674 ng/mL was used. The POD should then be divided by an UF of 30 (10 for human variation and 3 for animal-to-human extrapolation) to reach a target serum human level of 22.47 ng/mL. **Incorporating this target serum human level derived by NJDWQI for immunotoxicity effects into the NHDES MCL calculations results in a MCL for PFOS of 26 ppt (Table 3).**

Table 3. Impact of incorporating correct critical effects on NHDES proposed MCLs

	PFOA (ppt)	PFOS (ppt)
MCLs currently proposed by NHDES	38	70
MCLs if Macon et al., 2011 chosen as critical study for PFOA and Dong et al., 2009 chosen as critical study for PFOS	0.67	26
Full calculations can be found in Appendices 1 and 2.		

NHDES did not use appropriate uncertainty factors.

As stated in the Summary Report (NHDES 2019b), UFs are “adjustment factors used when knowledge about a chemical’s toxicity or effect on animal and human’s is

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incomplete." The UF for database limitations is inherently related to the choice of critical effect because it adjusts for the possibility of identifying a lower POD (or more sensitive effect) if additional studies were available. As stated above, we highly recommend NHDES base MCLs on the most sensitive endpoints (developmental delays in mammary gland development for PFOA and immunotoxicity for PFOS). However, should NHDES not support these recommendations, then we must call for the application of appropriate UFs.

The recommendations below are based on the PODs that have currently been proposed by NHDES as the critical effect for each chemical.

In the absence of basing the PFOA MCL on disrupted mammary gland development, NHDES should use a UF_{total}=300 to account for these sensitive effects. NHDES has proposed a UF_{total}=100 for PFOA based on:

- UF_A=10
- UF_H=3
- $UF_{other\ tox}$=3

The $UF_{other\ tox}$=3 was "applied due to evidence for associated effects on other physiological systems including immune function observed in animal and human epidemiological studies" (NHDES 2019b). However, applying this UF does not account for the effects on the mammary gland that occur at a POD more than 100-fold lower than the proposed POD.

For comparison, NJDWQI ultimately chose the same critical effect as NHDES has proposed, increased liver weight identified by (Loveless et al. 2006), and applied a $UF_{other\ tox}$=10 to account for "more sensitive effects, including delayed mammary gland development and hepatic toxicity after developmental exposures," that occurred at doses 100-fold lower than the LOAEL for increased liver weight (NJDWQI 2017). NHDES should use a $UF_{other\ tox}$=10 that would achieve a UF_{total}=300. **Applying an UF_{total}=300 to the NHDES MCL calculations results in a MCL for PFOA of 13 ppt (Table 4).**

In the absence of basing the PFOS MCL on immunotoxicity, NHDES should use a UF_{total}=300 to account for these sensitive effects. NHDES has proposed a UF_{total}=100 for PFOS based on:

- UF_A=10
- UF_H=3
- $UF_{other\ tox}$=3

The $UF_{othertox}$=3 was "applied due to concern for PFOS' effects on other physiological processes including the immune system (NTP 2016; and lipid metabolism (ATSDR

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2018).; Perkins et al. 2018)" (NHDES 2019b). Unfortunately, this $UF_{othertox}$ is not sufficient to be protective of the effects on the immune system.

For comparison, NJDWQI based the PFOS calculations on immunotoxicity, deriving a POD=674 ng/mL and applied a UF_{total}=30. This resulted in a target human serum level of 22.5 ng/mL (NJDWQI 2018). The target human serum level calculated by NHDES using UF_{total}=100 is 62.6 ng/mL, which is 2.8-fold higher than that calculated by NJDWQI, indicating that the UF was not protective enough. NHDES should use a $UF_{other\ tox}$=10 to achieve a UF_{total}=300. **Applying a UF_{total}=300 to the NHDES MCL calculations would reduce the target human serum level to 20.9 and would result in a MCL for PFOS of 24 ppt (Table 4).**

NHDES should use an UF_{total}=1000 for PFNA. NHDES has proposed a UF_{total}=300 for PFNA based on:

- UF_A=10
- UF_H=3
- $UF_{other\ tox}$=10

For comparison, NJDWQI ultimately chose the same critical effect as NHDES has proposed, increased liver weight in pregnant mice identified by (Das et al. 2015), but applied a UF_{total}=1000 based on an additional UF to account for the short duration of exposure (17 days) in the study chosen for development of the MCL and that other studies suggest that PFNA causes additional and/or more severe effects as exposure duration increases (NJDWQI 2015). NJDWQI ultimately applied the following UFs:

- UF_A=10
- UF_H=3
- $UF_{exposure\ duration}$=10
- $UF_{other\ tox}$=3

We recommend that NHDES follow NJDWQI in applying UFs to the derivation of a MCL for PFNA. **Applying an UF_{total}=1000 to the NHDES MCL calculations results in a MCL for PFNA of 7 ppt (Table 4).**

Table 4. Impact of incorporating correct UFs on NHDES proposed MCLs

	PFOA (ppt)	PFOS (ppt)	PFNA (ppt)

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MCLs currently proposed by NHDES	38	70	23
MCLs if correct UFs incorporated	13	24	7
Full calculations can be found in Appendices 1, 2, and 3.			

It can be noted that we agree with NHDES's decision to use an $UF_{other\ tox}$=10 for PFHxS, which NHDES used due to concerns over the limited number of studies conducted to date on PFHxS. It is also worth noting here that the study used to select the critical effect for PFHxS, Chang et al. 2018 only measured levels of thyroid stimulating hormone (TSH), not triiodothyronine (T3) or thyroxine (T4), and that the authors noted a significant increase in thyroid weight but did not state or show the magnitude of this effect (Chang et al. 2018). This is very concerning given that US EPA recently highlighted in the draft health assessment for another PFAS, PFBS, the importance of measuring these hormones due to the role they play in gestational and neonatal brain development and maturation (US EPA 2018). We hope that future work can address these limitations so that it can be determined if there are more sensitive critical effects and/or if an $UF_{other\ tox}$=10 is sufficient to be protective.

NHDES did not use the correct half-life value for PFNA.
For PFOA, PFOS, and PFHxS NHDES used half-life values from a study of non-occupationally exposed individuals in Sweden that was not yet available for inclusion in the analyses conducted by ATSDR (Li et al. 2018). This new study did not provide an analysis of PFNA. NHDES used the same PFNA half-life value that ATSDR used (Zhang et al. 2013).

NHDES must use the more representative half-life for PFNA as provided in Zhang et al. 2013. Zhang and colleagues calculated two half-life values for PFNA: 2.5 years for young females aged 50 years or less and 4.3 years for everyone else (adult males and females aged greater than 50 years) (Zhang et al. 2013). The shorter half-life for younger women is thought to reflect menstrual clearance of PFNA in this population of study participants. **Like ATSDR, NHDES chose to use the shorter half-life of 2.3 years for young, menstruating women, with no explanation for how this decision was made (ATSDR 2018).** It would be more protective of a larger majority of the population to use the longer half-life. NJDWQI also pointed this out, stating:

> *The estimates of PFNA half-life in women under 50 years of age are based on modeling of this pathway and are considered more uncertain than the estimates for men and older women. Although children were not included in this study, the increased excretion rate due to menstrual blood loss is not applicable to children. Similarly, the additional clearance through menstrual blood loss is not relevant to pregnant women.* (NJDWQI 2015)

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NHDES should use the half-life value for PFNA of 4.3 years unless they can provide adequate justification for using the shorter half-life. **Using the longer, more representative half-life for PFNA in the NHDES MCL calculations results in a MCL for PFNA of 13 ppt (Table 5).**

Table 5. Impact of incorporating correct half-life value on NHDES proposed MCLs

	PFNA (ppt)
MCL currently proposed by NHDES	23
MCL if the more representative half-life is incorporated	13
Full calculations can be found in Appendix 3.	

NHDES did not use the appropriate volume of distribution for PFHxS.
The volume of distribution (V_d) describes the degree to which a chemical is distributed in the body tissues versus in the blood plasma. For PFHxS, NHDES used the same V_d that ATSDR used (ATSDR 2018), which is based on a study conducted in Cynomolgus monkeys (Sundstrom et al. 2012). The estimates of V_d determined by Sundstrom et al., were sex-specific, with values of 0.287 and 0.213 L/kg for males and females, respectively. ATSDR chose to use the value of 0.287 for male animals, but did not provide additional rationale or support for this choice. NHDES used the same value. MN DH, however, in the recently released transgenerational toxicokinetic model for PFHxS used a V_d value of 0.25 L/kg, which is the average of the male and female values reported by Sundstrom et al., (MN DH 2019a). We suggest that it is most appropriate to use the most protective value that is available, that for females. **Incorporating this more protective V_d in the NHDES MCL calculations results in a MCL for PFHxS of 63 ppt (Table 6).**

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Table 6. Impact of incorporating correct half-life value on NHDES proposed MCLs

	PFHxS (ppt)
MCL currently proposed by NHDES	85
MCL if the most protective V_d is incorporated	63
Full calculations can be found in Appendix 4.	

Vulnerable populations and combined exposures

NH SB309 states "The commissioner shall adopt maximum contaminant levels (MCLs) that reasonably protect public health, **particularly prenatal and early childhood health**, and that are reasonably supported by peer reviewed science and independent or government agency studies." The need to particularly protect prenatal and early childhood health is because these life periods are the most sensitive periods to the long term impacts from PFAS exposure. Unfortunately, the MCLs currently proposed by NHDES fail to protect the most vulnerable among us - infants and those potentially exposed to these persistent and bioaccumulative chemicals for decades.

There are two reasons why this early life stage is particularly vulnerable to PFAS exposures. First, the fetal and early childhood life stages are the time the body's systems are being established and developed. Small changes that disrupt or permanently alter the course of development can increase the risk of later life disease. Second, infants and children consume more drinking water per unit body weight (US EPA 2000). Infants, for example may be exposed to PFAS via contaminated breast milk, and/or by infant formula prepared with PFAS contaminated water. NHDES can better estimate infant and childhood exposures by incorporating the use of the MN DH transgenerational toxicokinetic exposure model or by using the ingestion rate of 0.175 L/kg/day. The MCL values we have recommended incorporate the MN DH exposure model. It is important that these factors are adequately accounted for in the MCL calculation process, since developing children are both the most sensitive population as well as the population with the highest estimated exposure.

It is also important to recognize that some NH citizens have potentially been exposed to PFAS for many years or even decades. NH citizens are known to be exposed to PFOA, PFOS, PFNA, and PFHxS (Daly et al. 2018), but environmental testing indicates that citizens are also potentially exposed to several other PFAS including, but not limited to, PFBA, PFHpA, PFHxA, PFPeA, 6:2-Fluorotelomersulfonic acid. Given the persistence of PFAS in the environment and the long half-lives of PFAS in humans, chronically exposed citizens should also be considered a vulnerable population. Of particular

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concern is that citizens are exposed to complex mixtures of PFAS, some or all of which may impact the same biological systems. For example, at least seven PFAS have been associated with impacts on the immune system, liver, or development and reproduction (ATSDR 2018; NRDC 2019). MN DH has acknowledged the importance of mixtures of PFAS, which may act on similar health outcomes (Goeden et al. 2019). Specifically, MN DH stated:

> *PFAS commonly co-occur in drinking water and may have additive health effects. When multiple substances are present, MDH recommends evaluating the potential risk from the combined exposure. Evaluating a mixture of chemicals, based solely on individual [health based guidance values], may not provide an adequate margin of safety. MDH uses an additive approach, in which chemicals that share a common health endpoint (e.g., liver, developmental) are evaluated together.*

Likewise, NJDWQI has also noted that the modes of action and health effects are generally similar for PFAS, and acknowledged the possibility that the effects may be additive (NJDWQI 2015; 2017; 2018). In order to best protect the health of NH citizens, NHDES should also consider this possibility, as populations that are chronically exposed to a number of PFAS may be considered a sensitive population in need of extra protection.

Given the long half-life of many PFAS, the potential for PFAS to cause health concerns at low, environmentally relevant levels, and their extreme persistence in the environment, it is crucial that NHDES act to lower the MCLs and AGQS from what was initially proposed. Our comments have laid out several steps in the MCL process where more protective assumptions can and should be applied. These recommendations are scientifically justifiable and in line with those used by other US state agencies. NHDES should adopt these recommendations in order to comply with their charge to set MCLs that are protective of the most vulnerable, and indeed, of all NH citizens.

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Appendices

In Appendices 1-4, we have provided spreadsheets describing the values and calculations used in the MCL derivation process. The worksheets are broken into three parts: 1) the values that have been used or proposed for use by NHDES, NJDWQI, ATSDR, MN DH, and/or MI-DHHS; 2) the values from the tables presented in the comments that highlight the impacts of various recommendations we have made on an individual basis; 3) our overall recommendations which take into consideration the multiple changes that we have suggested. In Appendices 5-8, we have provided the various model parameters used by MN DH and MI-DHHS in applying the transgenerational toxicokinetic exposure model as well as the output graphs that plot the modeled serum concentration after exposure to a given water concentration for formula fed or breast fed infants. These data have also been submitted as attached Excel files.

Abbreviations used in the Appendices:

ATSDR	Agency for Toxic Substances and Disease Registry
Conc	Concentration
DAF	Dosimetric adjustment factor
DW	Drinking water
MCL	Maximum contaminant level
MDH	Minnesota Department of Health
MDHHS	Michigan Department of Health and Human Services
NHDES	New Hampshire Department of Environmental Services
NJDWQI	New Jersey Drinking Water Quality Institute
ppt	Parts per trillion
RfD	Reference Dose
RSC	Relative source contribution
UF	Uncertainty factor
Vd	Volume of distribution

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Appendix 1: Calculation of PFOA MCL

		Values from NHDES and other agencies					Impact of professional judgements made by NHDES as described in the comments				Our reccomendations	
		NHDES	NJDWQI	ATSDR	MDH	MDHHS	Table 1: infant specific exposure	Table 2: use of MDH exposure model	Table 3. mammary gland as critical effect	Table 4. UF to account for mammary gland effects	Based on MDH exposure model and mammary gland effects	Based on MDH exposure model and UF to account for mammary gland effects
serum level	ng/mL	4,351	4,351	8,290	38,000	8,290	4,351	4,351	**23**	4,351	**23**	4,351
Total UF	unitless	100	300	300	300	300	100	100	**30**	**300**	**30**	**300**
target human dose = animal serum dose / UF	=ng/mL	43.5	14.5	27.6	126.7	27.6	43.51	43.51	0.77	14.50	0.77	14.50
Vd	L/kg	0.17	0.17	0.2	0.17	0.2	0.17	0.17	0.17	0.17	0.17	0.17
half life	d	986	842	1400	840	840	986	986	986	986	986	986
DAF=Vd x ln(2)/half life	=L/kg/d	1.20E-04	1.40E-04	9.90E-05	1.40E-04	1.65E-04	1.20E-04	1.20E-04	1.20E-04	1.20E-04	1.20E-04	1.20E-04
RfD= target human dose x DAF x 1000	= ng/kg/day	5.2	2.0	2.7	17.8	4.6	5.2	5.2	0.1	1.7	0.1	1.7
RSC (%)		0.4	0.2	-	0.5	0.5	0.4	0.5	0.4	0.4	0.5	0.5
ingestion rate	L/kg/d	0.055	0.029	-	modeled	modeled*	**0.175**	**modeled**	0.055	0.055	**modeled**	**modeled**
MCL = RfD x RSC / ingestion	= ng/L	38	14	-	35	9	12	10	0.7	13	0.2	3

ATSDR did not calculate MCL values. *MDHHS used a Vd=0.2 in the model compared to Vd=0.17 used by

Values that have been changed from those proposed by NHDES are shown in **bold, larger** font.

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Appendix 2: Calculation of PFOS MCL

		Values from NHDES and other agencies					Impact of professional judgements made by NHDES as described in the comments				Our reccomendation
		NHDES	NJDWQI	ATSDR	MDH	MDHHS	Table 1. infant specific exposure	Table 2: use of MDH exposure model	Table 3. immunotox as critical effect	Table 4. UF to account for immunotox effects	Based on MDH exposure model and immunotox effects
serum level	ng/mL	6,260	674	7,430	2,360	7,430	6,260	6,260	**674**	6,260	**674**
Total UF	unitless	100	30	300	100	300	100	100	**30**	**300**	**30**
target human dose = animal serum dose / UF	=ng/mL	62.6	22.5	24.8	23.6	24.8	62.6	62.6	22.5	20.9	22.5
Vd	L/kg	0.23	0.23	0.2	0.23	0.2	0.23	0.23	0.23	0.23	0.23
half life	d	1241	1971	2000	1241	2000	1241	1241	1241	1241	1241
DAF=Vd x ln(2)/half life	=L/kg/d	1.28E-04	8.09E-05	6.93E-05	1.28E-04	6.93E-05	1.28E-04	1.28E-04	1.28E-04	1.28E-04	1.28E-04
RfD= target human dose x DAF x 1000	= ng/kg/day	8.0	1.8	1.7	3.0	1.7	8.0	8.0	2.9	2.7	2.9
RSC (%)		0.5	0.2	-	0.5	0.5	0.5	0.5	0.5	0.5	0.5
ingestion rate	L/kg/d	0.055	0.029	-	modeled	modeled**	**0.175**	**modeled**	0.055	0.055	**modeled**
MCL = RfD x RSC / ingestion	= ng/L	70*	13	-	15	8	23	38	26	24	13

*NHDES rounded the PFOS value to 70 from 73. ATSDR did not calculate MCL values. **MDHHS used placental transfter and breast milk transfer values of 0.043 and 0.013, respectivly, and Vd=0.2 whereas MDH used values of 0.04 and 0.017 and Vd=0.23.

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Appendix 3: Calculation of PFNA MCL

		Values from NHDES and other agencies				Impact of professional judgements made by NHDES as described in the comments				Our reccomendation
		NHDES	NJDWQI	ATSDR	MDHHS	Table 1. infant specific exposure	Table 2: use of MDH exposure model	Table 4. UF to account for short exposure scenario	Table 5. different half life	Based on MDH exposure model, additioanl UF, and different half life
serum level	ng/mL	4,900	4,900	10,900	6,800	4,900	4,900	4,900	4,900	4,900
Total UF	unitless	300	1000	300	300	300	300	**1000**	300	**1000**
target human dose = animal serum dose / UF	=ng/mL	16.3	4.9	36.3	22.7	16.3	16.3	4.9	16.3	4.9
Vd	L/kg	0.2	-	0.2	0.2	0.2	0.2	0.2	0.2	0.2
half life	d	900	-	900	900	900	900	900	**1570**	**1570**
DAF=Vd x ln(2)/half life	=L/kg/d	1.54E-04	-	1.54E-04	1.54E-04	1.54E-04	1.54E-04	1.54E-04	8.83E-05	8.83E-05
RfD= target human dose x DAF x 1000	= ng/kg/day	2.5	-	3.0	3.0	2.5	2.5	0.8	1.4	0.4
RSC (%)		0.5	0.5	-	0.5	0.5	0.5	0.5	0.5	0.5
ingestion rate	L/kg/d	0.055	-	-	modeled**	**0.175**	**modeled**	0.055	0.055	**0.175**
MCL = RfD x RSC / ingestion	= ng/L	23	13*	-	9	7	7	7	13	1

*NJ arrived at this number by multiplying the target human dose (4.9 ng/mL) by the RSC of 0.5 to get 2500 ng/L. They then stated that there is a 200:1 serum to drinking water ratio. So, 2500 ng/L / 200 = 12.5 ng/L rounded to 13 ng/L. ATSDR did not calculate MCL values. **MDH did not provide values for placental or breast milk transfer. The values for these parameters are found in the MDHHS document.

Values that have been changed from those proposed by NHDES are shown in **bold, larger** font.

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Appendix 4: Calculation of PFHxS MCL

		Values from NHDES and other agencies				Impact of professional judgements made by NHDES as described in the comments			Our reccomendation
		NHDES	ATSDR	MDH	MDHHS	Table 1. infant sepecifc exposure	Table 2: use of MDH exposure model	Table 6. different Vd	Based on MDH exposure model and different Vd
serum level	ng/mL	27,200	73,220	32,400	73,220	27,200	27,200	27,200	27,200
Total UF	unitless	300	300	300	300	300	300	300	300
target human dose = animal serum dose / UF	=ng/mL	90.7	244.1	108.0	244.1	90.7	90.7	90.7	90.7
Vd	L/kg	0.287	0.287	0.25	0.287	0.287	0.287	**0.213**	**0.213**
half life	d	1935	3100	1935	3100	1935	1935	1935	1935
DAF=Vd x ln(2)/half life	=L/kg/d	1.03E-04	6.42E-05	8.96E-05	6.42E-05	1.03E-04	1.03E-04	7.63E-05	7.63E-05
RfD= target human dose x DAF x 1000	= ng/kg/day	9.3	20.0	9.7	15.7	9.3	9.3	6.9	6.9
RSC (%)		0.5	-	0.5	0.5	0.5	0.5	0.5	0.5
ingestion rate	L/kg/d	0.055	-	modeled	modeled*	**0.175**	**modeled**	0.055	**modeled**
MCL = RfD x RSC / ingestion	= ng/L	85	-	47	84	27	44	63	30

ATSDR did not calculate MCL values.
*MDHHS used placental transfter and breast milk transfer values of 0.8 and 0.012, respectivly, and Vd=0.287 whereas MDH used values of 0.7 and 0.014 and Vd=0.25.

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Appendix 5: Application of MN DH transgenerational toxicokinetic exposure model to PFOA

	MDH	MDHHS	NHDES proposed values	NHDES our reccomended values
half life (days)	840	840	986	986
Placental transfer (infant:maternal serum)	0.87	0.87	0.87	0.87
Breast Milk transfer (maternal milk:serum)	0.052	0.052	0.052	0.052
Volume of Distribution (Vd) (L/kg)	0.17	0.2	0.17	0.17
POD serum level (mg/L)	38	8.29	4.351	**0.023**
UF	300	300	100	**30**
Target serum concentration (mg/L)	0.13	0.0276	0.044	0.000767
modeled DW conc for formula fed infants (ug/L)	0.15	-	0.026	0.0004
corresponding MCL (ppt)	150	-	26	0.4
modeled DW conc for breastfed infants (ug/L)	0.035	0.009	0.01	0.00017
corresponding MCL (ppt)	35	9	10	0.17

MDHHS only provided values for breastfed infants.
Values that have been changed from those proposed by NHDES are shown in **bold, larger** font.

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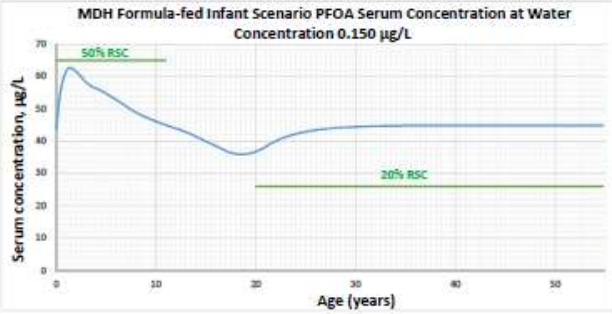
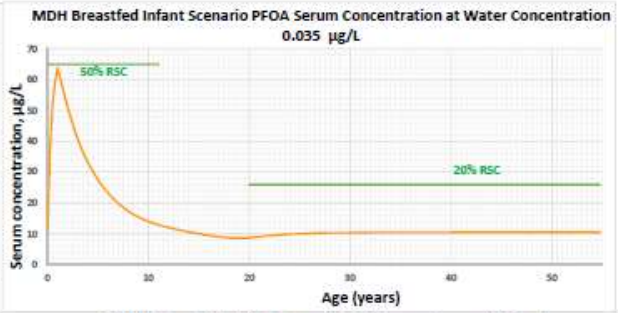
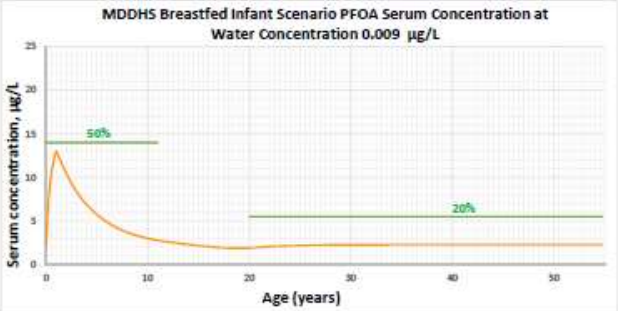
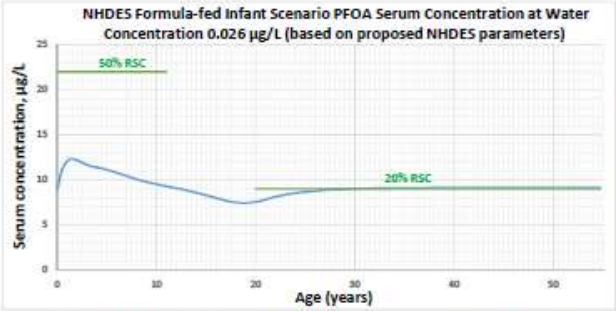
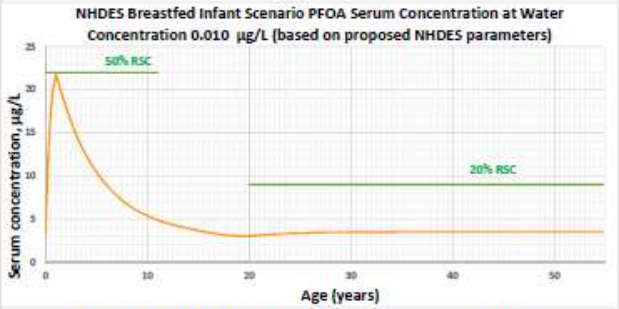
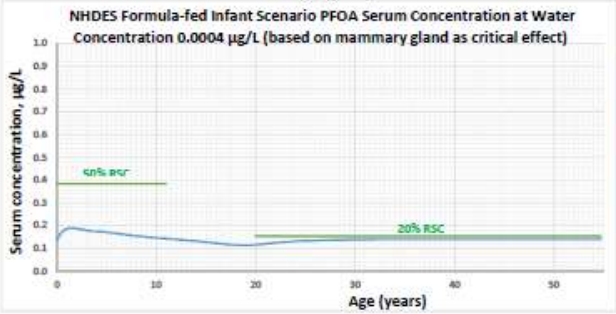

MDH Formula-fed Infant Scenario PFOA Serum Concentration at Water Concentration 0.150 µg/L
50% RSC
20% RSC
Serum concentration, µg/L
Age (years)

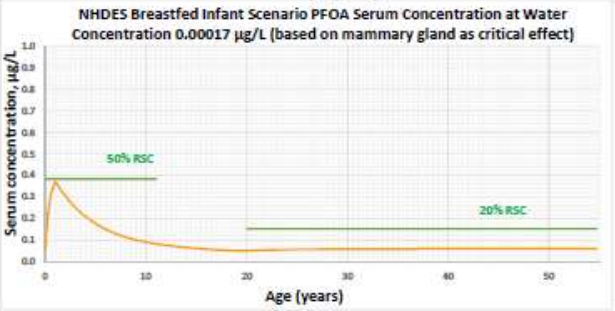

MDH Breastfed Infant Scenario PFOA Serum Concentration at Water Concentration 0.035 µg/L
50% RSC
20% RSC
Serum concentration, µg/L
Age (years)


MDDHS Breastfed Infant Scenario PFOA Serum Concentration at Water Concentration 0.009 µg/L
50%
20%
Serum concentration, µg/L
Age (years)


NHDES Formula-fed Infant Scenario PFOA Serum Concentration at Water Concentration 0.026 µg/L (based on proposed NHDES parameters)
50% RSC
20% RSC
Serum concentration, µg/L
Age (years)


NHDES Breastfed Infant Scenario PFOA Serum Concentration at Water Concentration 0.010 µg/L (based on proposed NHDES parameters)
50% RSC
20% RSC
Serum concentration, µg/L
Age (years)


NHDES Formula-fed Infant Scenario PFOA Serum Concentration at Water Concentration 0.0004 µg/L (based on mammary gland as critical effect)
50% RSC
20% RSC
Serum concentration, µg/L
Age (years)


NHDES Breastfed Infant Scenario PFOA Serum Concentration at Water Concentration 0.00017 µg/L (based on mammary gland as critical effect)
50% RSC
20% RSC
Serum concentration, µg/L
Age (years)

Appendix 6: Application of MN DH transgenerational toxicokinetic exposure model to PFOS

	MDH	MDHHS	NHDES proposed values	NHDES our reccomended values
half life (days)	1241	2000	1241	1241
Placental transfer (infant:maternal serum)	0.4	0.43	0.4	0.4
Breast Milk transfer (maternal milk:serum)	0.017	0.013	0.017	0.017
Volume of Distribution (Vd) (L/kg)	0.23	0.2	0.23	0.23
POD serum level (mg/L)	2.36	7.43	6.26	**0.674**
UF	100	300	100	**30**
Target serum concentration (mg/L)	0.0236	0.0248	0.0626	0.0225
modeled DW conc for formula fed infants (ug/L)	0.036	-	0.04	0.013
corresponding MCL (ppt)	36	-	40	13
modeled DW conc for breastfed infants (ug/L)	0.015	0.008	0.038	0.013
corresponding MCL (ppt)	15	8	38	13

MDHHS only provided values for breastfed infants.
Values that have been changed from those proposed by NHDES are shown in **bold, larger** font.

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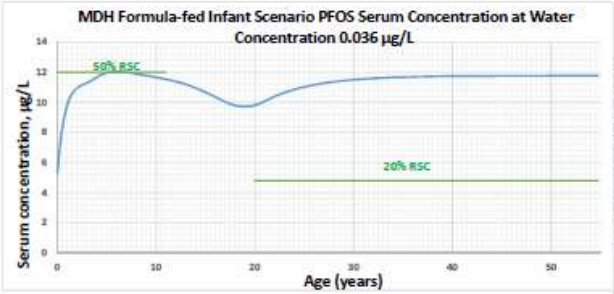
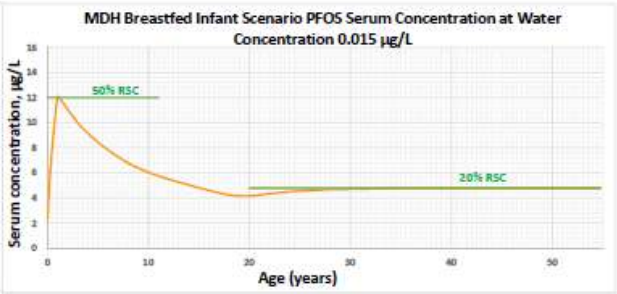
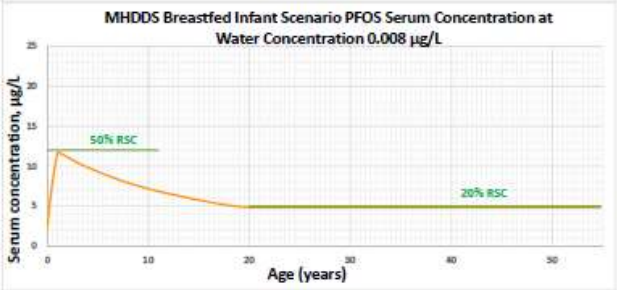
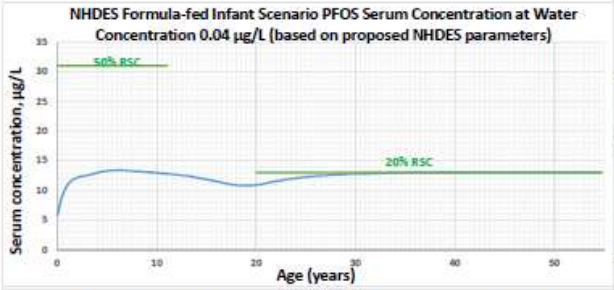
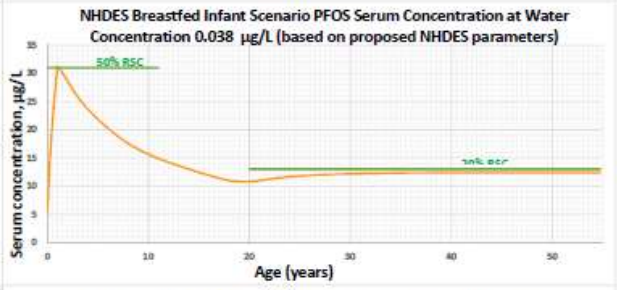
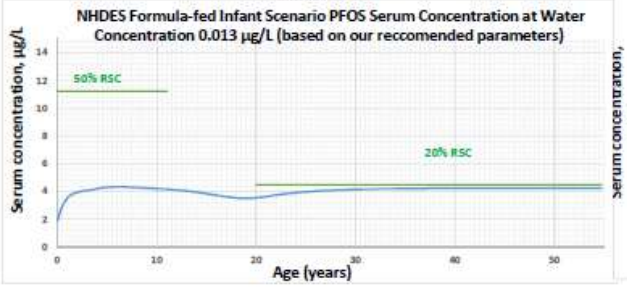

MDH Formula-fed Infant Scenario PFOS Serum Concentration at Water Concentration 0.036 µg/L
Serum concentration, µg/L
Age (years)
50% RSC
20% RSC

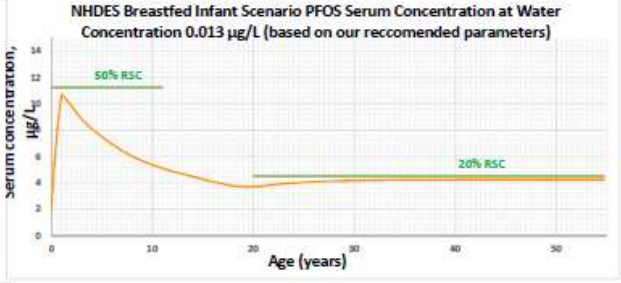

MDH Breastfed Infant Scenario PFOS Serum Concentration at Water Concentration 0.015 µg/L
Serum concentration, µg/L
Age (years)
50% RSC
20% RSC


MHDDS Breastfed Infant Scenario PFOS Serum Concentration at Water Concentration 0.008 µg/L
Serum concentration, µg/L
Age (years)
50% RSC
20% RSC


NHDES Formula-fed Infant Scenario PFOS Serum Concentration at Water Concentration 0.04 µg/L (based on proposed NHDES parameters)
Serum concentration, µg/L
Age (years)
50% RSC
20% RSC


NHDES Breastfed Infant Scenario PFOS Serum Concentration at Water Concentration 0.038 µg/L (based on proposed NHDES parameters)
Serum concentration, µg/L
Age (years)
50% RSC


NHDES Formula-fed Infant Scenario PFOS Serum Concentration at Water Concentration 0.013 µg/L (based on our reccomended parameters)
Serum concentration, µg/L
Age (years)
50% RSC
20% RSC


NHDES Breastfed Infant Scenario PFOS Serum Concentration at Water Concentration 0.013 µg/L (based on our reccomended parameters)
Age (years)
50% RSC
20% RSC

Appendix 7: Application of MN DH transgenerational toxicokinetic exposure model to PFNA

	MDH	MDHHS	NHDES proposed values	NHDES our reccomended values
half life (days)	-	900	900	**1570**
Placental transfer (infant:maternal serum)	-	0.69	0.69	0.69
Breast Milk transfer (maternal milk:serum)	-	0.032	0.032	0.032
Volume of Distribution (Vd) (L/kg)	-	0.2	0.2	0.2
POD serum level (mg/L)	-	6.8	4.9	4.9
UF	-	300	300	**1000**
Target serum concentration (mg/L)	-	0.0227	0.0163	0.0049
modeled DW conc for formula fed infants (ug/L)	-	-	0.012	0.002
corresponding MCL (ppt)	-	-	12	2
modeled DW conc for breastfed infants (ug/L)	-	0.009	0.007	0.001
corresponding MCL (ppt)	-	9	7	1

MDH has not provided values for PFNA. MDHHS only provided values for breastfed infants. Values that have been changed from those proposed by NHDES are shown in **bold, larger** font.

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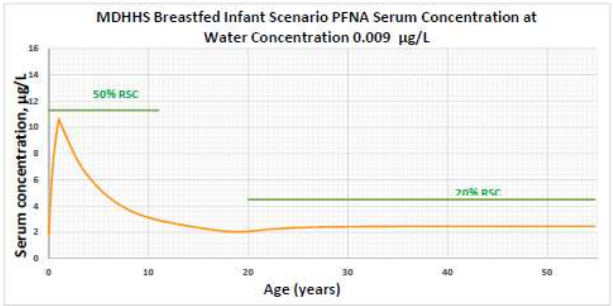
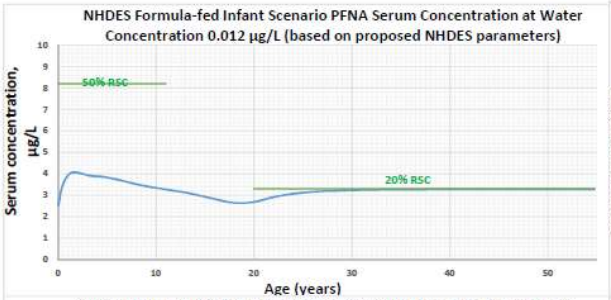
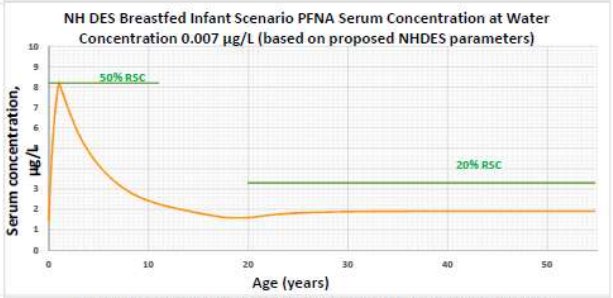
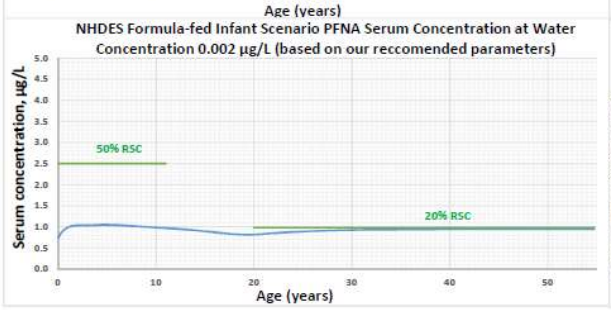
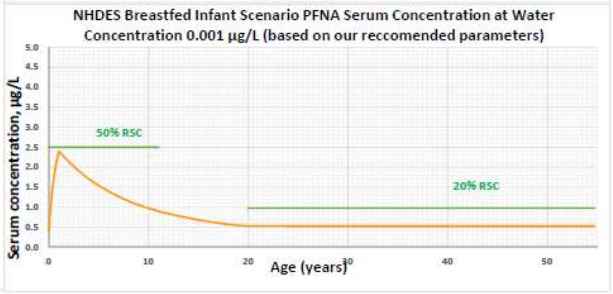

MDHHS Breastfed Infant Scenario PFNA Serum Concentration at Water Concentration 0.009 µg/L
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Formula-fed Infant Scenario PFNA Serum Concentration at Water Concentration 0.012 µg/L (based on proposed NHDES parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NH DES Breastfed Infant Scenario PFNA Serum Concentration at Water Concentration 0.007 µg/L (based on proposed NHDES parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Formula-fed Infant Scenario PFNA Serum Concentration at Water Concentration 0.002 µg/L (based on our reccomended parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Breastfed Infant Scenario PFNA Serum Concentration at Water Concentration 0.001 µg/L (based on our reccomended parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)

Appendix 8: Application of MN DH transgenerational toxicokinetic exposure model to PFHxS

	MDH	MDHHS	NHDES proposed values	NHDES our reccomended values
half life (days)	1935	3100	1935	1935
Placental transfer (infant:maternal serum)	0.7	0.8	0.7	0.7
Breast Milk transfer (maternal milk:serum)	0.014	0.012	0.014	0.014
Volume of Distribution (Vd) (L/kg)	0.25	0.287	0.287	**0.213**
POD serum level (mg/L)	32.4	73.22	27.2	27.2
UF	300	300	300	300
Target serum concentration (mg/L)	0.108	0.244	0.091	0.091
modeled DW conc for formula fed infants (ug/L)	0.108	-	0.044	0.033
corresponding MCL (ppt)	108	-	44	33
modeled DW conc for breastfed infants (ug/L)	0.047	0.084	0.049	0.030
corresponding MCL (ppt)	47	84	49	30

MDHHS only provided values for breastfed infants.
Values that have been changed from those proposed by NHDES are shown in **bold, larger** font.

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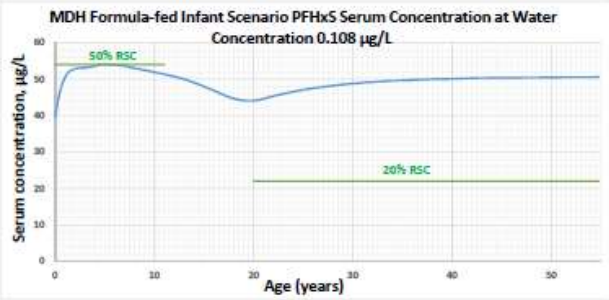
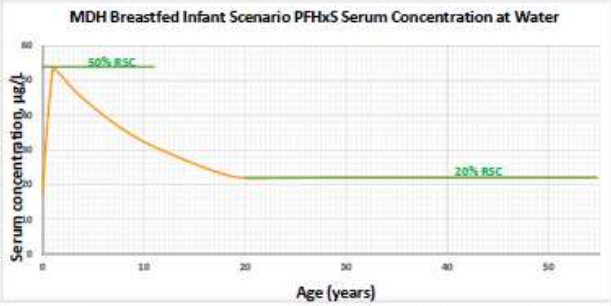
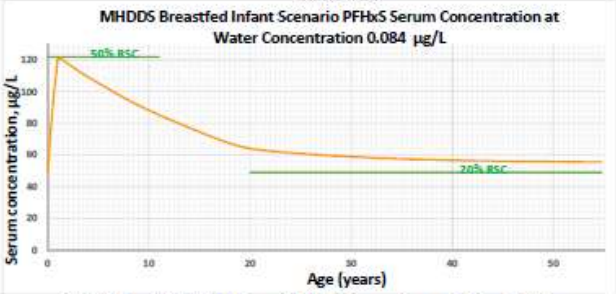
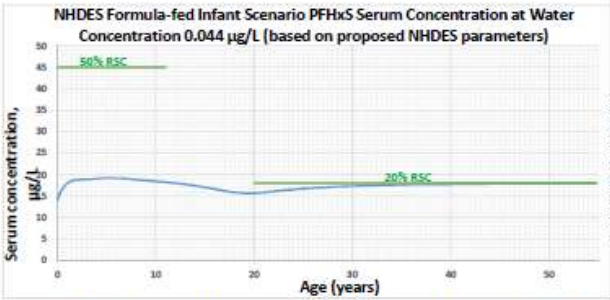
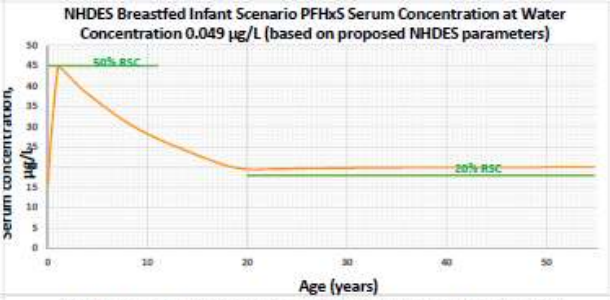
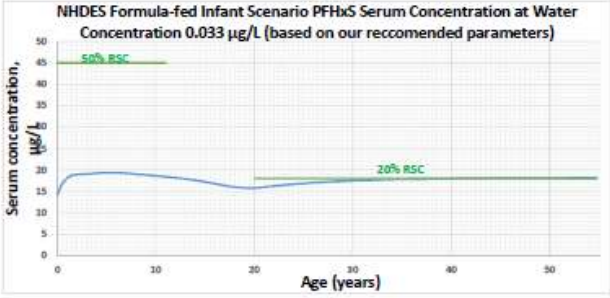

MDH Formula-fed Infant Scenario PFHxS Serum Concentration at Water Concentration 0.108 µg/L
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)

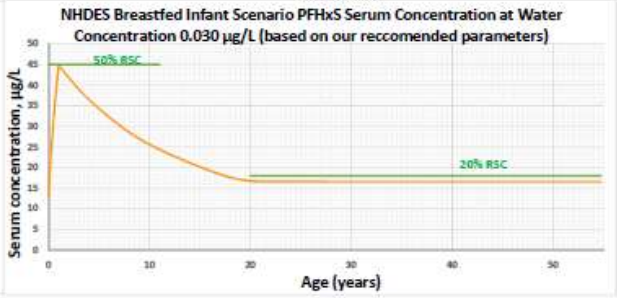

MDH Breastfed Infant Scenario PFHxS Serum Concentration at Water
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


MHDDS Breastfed Infant Scenario PFHxS Serum Concentration at Water Concentration 0.084 µg/L
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Formula-fed Infant Scenario PFHxS Serum Concentration at Water Concentration 0.044 µg/L (based on proposed NHDES parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Breastfed Infant Scenario PFHxS Serum Concentration at Water Concentration 0.049 µg/L (based on proposed NHDES parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Formula-fed Infant Scenario PFHxS Serum Concentration at Water Concentration 0.033 µg/L (based on our reccomended parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)


NHDES Breastfed Infant Scenario PFHxS Serum Concentration at Water Concentration 0.030 µg/L (based on our reccomended parameters)
Serum concentration, µg/L
50% RSC
20% RSC
Age (years)