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Re: Setting Public Drinking Water and Groundwater Standards for PFOA, PFOS, PFNA, & PFHxS

On behalf of The Endocrine Disruption Exchange (TEDX), we appreciate this opportunity to submit comments in support of NHDES Stakeholder and Technical Work Sessions regarding setting 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.

We appreciate NHDES taking this important step to protect the citizens of New Hampshire and value that NHDES is seeking stakeholder involvement and public comment to set maximum contaminant levels (MCLs). 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 MCLs for drinking water 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.

We are very encouraged to hear that NHDES is looking for guidance on which studies to consider when setting MCLs. We support NH DES looking to the recently released ATSDR Toxicological Profile on Perfluoroalkyls, Draft for Public Comment (June 2018) [1] and to states such as Vermont and New Jersey that have recently evaluated these same contaminants. The June 2018 ATSDR report includes new studies not previously considered in earlier drafts or the Lifetime Health Advisories and Health Effects Support Documents for Perfluorooctanoic Acid and Perfluorooctane Sulfonate (May 2016) prepared by the US EPA, and therefore derives lower minimum risk levels (MRL) that are more health protective. While we applaud the efforts of the ATSDR in collecting, examining, summarizing and interpreting the available data on select PFASs we feel that there were several key improvements that could be made, and which NHDES should consider in order to set MCLs that will provide adequate protection for New Hampshire residents. Our comments are provided below.

1. **Exposure estimates must be made to protect the most sensitive populations.** Developing children are the most at risk of the long term effects from PFAS exposure. There are two reasons for this. 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, children and pregnant women consume more drinking water per unit body weight [2]. Infants, for example may be exposed to PFAS via contaminated breastmilk, and/or by infant

formula prepared with PFAS contaminated water. 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.

To date, only Vermont and Minnesota have used drinking water exposure factors to protect a child less than one year of age. Vermont, however used a more protective relative source contribution (RSC) (20%) than Minnesota (50%). US EPA used drinking water exposure estimates to account for pregnant and lactating women (0.054 L/kg/day) when setting the PFOA and PFOS health advisory limits. New Jersey used the least protective exposure factors, those for adults (0.029 L/kg/day), when proposing MCLs. To protect the citizens of New Hampshire, it is imperative that NHDES use the most protective exposure estimates, that for a child less than one year of age (0.175 L/kg/day), with a 20% RSC when setting MCLs.

2. **The MCL for PFOA should be <1 ppt or no more than 3 ppt. These MCLs result when the most sensitive health outcomes are chosen with consideration of protecting those with the greatest sensitivity and highest estimated exposure.** Delayed development of the mammary gland is the most sensitive endpoint in response to PFOA exposure and should be used as the critical endpoint for deriving a reference dose (RfD). Delayed mammary gland development has been observed in several independent studies from the National Toxicology Program and is a consistent finding across different strains of mice and different windows of exposure [3-5]. The ATSDR stated that there were no adverse changes to the mammary gland, citing a lack of evidence for an effect on lactation. However, mice exposed to PFOA during their pregnancy displayed delayed mammary gland involution and changes in milk protein gene expression [5, 6]. The lack of changes in pup body weight following these pregnancy related mammary gland changes is not enough evidence to conclude there was no adverse effect, as compensatory mechanisms like increased nursing duration or events could have occurred. Furthermore, ATSDR failed to recognize the structural changes in development of the mammary gland following prenatal exposure to PFOA as adverse. Delays such as these increase the sensitivity of the mammary gland to later life carcinogenic exposures, thereby increasing the risk for breast cancer [7-9].

   Both ATSDR and the New Jersey Drinking Water Quality Institute (NJDWQI) [10] identified delays in mammary gland development as the most sensitive endpoint, but stopped short of using it in their final calculations. Instead, ATSDR used the neurodevelopmental [11] and skeletal effects [12] as critical endpoints to calculate a RfD. ATSDR did not include an uncertainty factor to account for the effects on mammary gland that happen at lower doses. Though the ATSDR document stops short of incorporating drinking water exposure estimates that lead to a MCL, we estimate that based on the draft ATSDR MRL, the MCL based on neurodevelopmental and skeletal effects would be 3 ppt using the more protective drinking water estimate for a child less than one year of age (0.175 L/kg/day) and RSC=20%.

   In contrast, NJDWQI went a step further and calculated a RfD for mammary gland effects (0.11 ng/kg/day), though they ultimately decided against using it, citing that there is as of

yet no precedence for using mammary gland effects in quantitative risk assessment [10]. Instead, NJDWQI choose to base the MCL on increased liver weight and applied an uncertainty factor to account for the effects on the mammary gland and other outcomes that occur at lower doses [13]. The resulting MCL calculated by NJDWQI was 14 ppt. The MCL derived by NJDWQI would have been lower (i.e. 2 ppt) had they chosen to base their assumed exposure factor on a more sensitive and more highly exposed population (child less than one year of age (0.175 L/kg/day)) rather than an adult (0.029 L/kg/day).

We argue that we must use the most sensitive outcome (delayed mammary gland development) and the most protective exposure assessment (a child less than one year of age) to set a health protective MCL for the residents of New Hampshire. NJDWQI calculated a reference dose (RfD) of 0.11 ng/kg/day for mammary gland effects based on Macon et al. 2011 ([4]). With this RfD, a proposed MCL based on exposure estimates for a child less than one year of age and RSC=20% is 0.13 ppt.

3. **The MCL for PFOS should be <1 ppt or no more than 2 ppt. These MCLs result when the most sensitive health outcomes are chosen with consideration of protecting those with the greatest sensitivity and highest estimated exposure.** Effects on the immune system are the most sensitive health outcome for PFOS. The National Toxicology Program (NTP) recently completed a systematic review of the human epidemiological and animal mechanistic evidence linking PFOS and PFOA to immune effects and concluded that PFOS and PFOA are "presumed to be an immune hazard to humans." The NTP concluded that PFOS suppresses the antibody response, disease resistance, and natural killer cell activity [14].

   The NJDWQI choose the 2009 study by Dong et al., which reported a decreased immune response to sheep red blood cell antigen (sRBC) as the critical study for setting the MCL for PFOS [15, 16], deriving a RfD of 1.8 ng/kg/day. The resulting MCL of 13 ppt was reached using the exposure estimate for adults instead of the more protective estimate for a child less than one year of age. Had the more protective drinking water exposure estimates been used, the resulting MCL would be 2 ppt.

   On the other hand, the ATSDR report acknowledged that adverse immune effects occur at very low doses, but because the immune studies were performed in strains of mice for which pharmacokinetic model parameters were lacking, the studies could not be used in the Wambaugh et al. (2013) pharmacokinetic model [17] that was used to estimate time weighted average serum concentrations from certain dose and exposure duration scenarios. Therefore, the immune studies were not chosen for deriving the MRL. Instead, ATSDR applied a modifying factor of 10 to account for the adverse effects on the immune system that occur at doses lower than the study that was used to derive the MRL of $2x10^{-6}$ mg/kg/day. Using the most protective exposure estimates, that for a child less than one year of age and RSC=20%, the ATSDR provisional MRL translates to a proposed MCL of 2 ppt. However, ATSDR did note that serum levels of PFOS were available for the immune studies with effects at low doses. Therefore, ATSDR could have used the trapezoid rule to calculate

the time weighted average serum levels for these studies, as they did for PFNA and PFHxS. In fact, ATSDR did this for one immune study, calculating a candidate MRL for Dong et al. 2011, though they stopped short of calculating candidate MRLs for the other immune studies. The choice of Dong et al. 2011, the study with the highest LOAEL, on which to derive a candidate MRL on is inconsistent with ATSDR's practice of choosing the study with the lowest LOAEL when selecting the principle study for MRL derivation. For example, using the same uncertainty factors as ATSDR used to calculate a candidate MRL based on Dong et al. 2011, and the most protective drinking water exposure estimates, proposed MCLs based on Dong et al. 2009, Guruge et al. 2009, or Peden-Adams et al. would be 0.89, 0.25, or 0.02 ppt, respectively.

4. **The MCL for PFNA should not be more than 2 ppt. This MCL results when the most representative half-life for PFNA is used in the pharmacokinetic model and there is consideration for protecting those with the greatest sensitivity and highest estimated exposure.** Compared to PFOA and PFOS, there is less data available for PFNA that is amenable to deriving a MCL. Because PFNA has not yet been studied as extensively as PFOA and PFOS, it is unknown if will also cause developmental effects, including on the mammary gland and immune system, at low doses. However, PFNA does have an *in vitro* profile that looks very similar to that of PFOA [18]. Importantly, ATSDR incorrectly underestimated the half-life of PFNA, which influences the calculation of the first order one-compartment model parameter k_e. In the Zhang et al. 2013 paper, two different half-life values were derived: one of 900 days for young women and one of 1,570 days for everyone else. ATSDR provided no rationale why one half-life was chosen over the other, but it makes more sense to use the longer half-life, which represents a larger population and would result in a more protective MRL value. When the longer half-life is used, the resulting MRL is 2×10^{-6} mg/kg/day, which translates to a proposed MCL of 2 ppt using the most protective drinking water exposure estimates for a child less than one year of age and RSC=20%.

5. **The MCL for PFHxS should not be more than 2 ppt. This MCL results when new data indicating effects on thyroid hormone signaling are considered and accounted for with an additional uncertainty factor.** Like PFNA, PFHxS is also less well studied than PFOA and PFOS, though several similarities are noted. For example, Butenhoff et al. (2009) observed increased liver weight, hepatocellular hypertrophy and decreased serum cholesterol and triglycerides [19]. This profile mirrors what has been observed for PFOA (see A-14). Vermont and Minnesota have both regulated PFHxS based on similarity to PFOS.

   ATSDR estimated the time weighted average serum concentration of PFHxS as 73.22 μg/mL. This leads to a $NOAEL_{HED}$ = 0.0047 mg/kg/day and a provisional MRL = 2×10^{-5} mg/kg/day. This then translates to a proposed MCL of 18 ppt when the most protective drinking water estimate for a child under one year of age is applied.

However, new research published this year from Ramhoj et al., demonstrates that exposure to PFHxS during pregnancy results in marked decreases in serum thyroxine (T4) in exposed dams and offspring [20]. Thyroxine is critical for directing proper brain development [21, 22]. The LOAEL observed in this study is 5 mg/kg/day and the NOAEL is 0.5 mg/kg/day. Unfortunately, the study authors only determined serum PFHxS concentrations in animals exposed to 25 and 45 mg/kg/day. Thus, this data is not likely amenable to use in deriving a human equivalent point of departure (POD_{HED}), but it would be prudent to apply an additional uncertainty factor of 10 to account for these effects that occur at lower doses. Doing so would reduce the proposed MCL to 2 ppt using the most protective drinking water estimates, that for a child less than one year of age and RSC=20%.

6. **NHDES should use a class-based approach for PFASs, especially those that have insufficient data to calculate a MRL on their own.** New Hampshire residents are known to be exposed to PFOA, PFOS, PFNA, and PFHxS [23], 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. The current effort to only set MCLs for four PFASs may leave New Hampshire residents at risk due to exposure to other, non-regulated PFASs. There is a growing push across the US for states and the US EPA to address and regulate PFASs as a class, especially as PFASs are related in their extreme environmental persistence. NHDES should look to states like Vermont who have already taken steps to address data-poor PFASs based on class similarity to PFOA and PFOS [24]. This summer Vermont added PFHxS, PFHpA and PFNA to the health advisory based on the similarity of these chemicals to PFOA and PFOS. NHDES should follow Vermont's lead and propose MCL levels for all PFAS that have been detected in the drinking, ground and surface water or air of New Hampshire based on the similarity that these chemicals show to other PFAS like PFOA, PFOS.

   At a minimum, NHDES should consider the potential for additive toxicity among the PFAS that New Hampshire residents are exposed to. These PFASs are known to impact similar endpoints across *in vitro, in vivo*, and epidemiological studies. Many of the health effects for these PFASs are well described in Chapter 2 of the ATSDR report [1]. NJDWQI noted that the modes of action and health effects are generally similar for PFAS, and acknowledged the possibility that the effects may be additive [13]. In order to best protect the health of New Hampshire residents, 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. We strongly encourage NHDES to consider a class-based approach to regulating PFAS in drinking water given the potential for exposure to multiple PFAS and the possibility for additive effects

The recommendations that we have made in our comments are in line with what is currently detectable and treatable. Many laboratories using EPA Method 537 can detect <1 ppt, and most method reporting limits, including those of Eurofins Eaton Analytical are at 2 ppt [25, 26]. We also

recommend that NHDES consider using the Total Oxidizable Precursor Assay (TOPA), an analytical technique for total perfluoroalkyl acid (PFAA) precursors. It is estimated the current efforts using analytical techniques similar to EPA Method 537 are only able to detect 30-50% of the total PFAAs and PFAA precursors present in areas contaminated with PFAS from aqueous film forming foam, thus indicating that we are severely underestimating potential exposure [27]. The TOPA assay would not only provide an estimate of total PFAS in a sample, which would be useful if PFAS were to be regulated as a class, but it would also improve our understanding of potential environmental risks due to PFAS. Effective technologies are available to treat PFAS-contaminated water, including granular activated carbon, which has been demonstrated to remove PFOA, PFOS, PFNA and PFHxS to below detection limits.

NHDES is not alone in its efforts to set MCLs for drinking and/or ground water. Other states, such as Michigan and New York, are also moving in this direction, whereas New Jersey, Vermont, and Minnesota already have regulations in place. New Hampshire has the opportunity to show itself as a leader in protecting its citizens from the harmful effects attributed to these chemicals. There is no doubt that many states will look to New Hampshire for guidance as they too adopt rules to regulate PFAS. The literature on PFAS is growing exponentially. As our understanding of the most sensitive health endpoints continues to grow, there is no doubt that health effects will be observed at even lower doses than the ones currently known today, especially for PFNA and PFHxS. It is crucial, therefore, that New Hampshire set the most health protective MCLs possible. The alternative, should less protective MCLs be adopted, is that NHDES will be pushed to adopt lower levels in three years when the law is reevaluated, which would ultimately be costlier to New Hampshire water treatment systems.

We look forward to reviewing the draft guidelines and providing further guidance and comments once a draft document is available.

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