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

We applaud New Hampshire Department of Environmental Services for initiating the process of developing drinking water and groundwater standards for PFOA, PFOS, PFNA, and PFHxS. We appreciate this opportunity to provide technical input.

These comments are submitted on behalf of the STEEP project, an inter-institutional research center funded by the NIEHS Superfund Research Program (https://web.uri.edu/steep/). As part of the STEEP mission, our team is committed to addressing the ubiquitous human health impacts of PFAS exposures through rigorous interdisciplinary science, community engagement and outreach, development of novel detection techniques, and redefinition of dose exposure benchmarks. Our Superfund center includes researchers from University of Rhode Island, Harvard T.H. Chan School of Public Health, and Silent Spring Institute studying environmental fate and transport and human exposure to poly- and perfluoroalkyl substances (PFASs).

Our comments are summarized below.

Epidemiological evidence should be given greater consideration when establishing risk levels. While ATSDR draft Toxicological Profile refers to over 600 reports on PFAS toxicity, with over 400 of them being human studies, the present version should be able to rely much more on the epidemiology evidence. That is not the case, and we believe that this is problematic. We agree with senior scientists from the U.S. EPA (Gwinn et al. 2017), who recently argued that risk assessment had gone wrong in several cases due to the narrow focus on animal toxicology, and they recommended a more comprehensive review.

The ATSDR draft argues that epidemiology studies are not consistent. We agree that they are often not, but it would have been very surprising if they were, given natural variability and the impact of different settings. The draft describes the differences but does not attempt to decipher why such differences occur (e.g., exposure and/or outcome assessment at different times).

We understand that ATSDR, due to the mentioned weaknesses, has refrained from calculating or citing benchmark dose (BMD) calculations for human data. However, as the weaknesses have been exaggerated in our minds, we believe that it is a mistake to disregard human data. We note that the European Food Safety Authority (EFSA) has carried out such calculations and use them

for derivation of tolerable weekly intake levels (EFSA 2018). However, EFSA used groupings of data, e.g., quartiles, and therefore assumed that no effect occurred in the lowest group (quartile) and therefore overestimated the BMD levels. Our BMD calculations (Budtz-Jørgensen and Grandjean 2018), which were based on antibody response to immunizations in two birth cohorts in the Faroe Islands, suggest that the new MRLs calculated by ATSDR are perhaps as much as 10-fold above exposure limits that would be fully protective. Given that serum concentrations of PFASs are never too closely correlated, studies show that mutual adjustment is possible. In our view, epidemiological studies should not be dismissed due to the fact that exposures are always mixed.

Mammary gland development is a sensitive endpoint for PFOA toxicity. Studies in rodents have shown that low dose PFOA exposures can impair mammary gland development (Macon et al 2011, Tucker et al. 2015, White et al. 2007, White et al. 2011). Altered mammary gland development associated with low dose PFOA exposure is concerning because of the potential to disrupt lactation. PFOA exposure in mice was associated with reduced mammary differentiation and altered milk protein gene expression (White et al. 2007). In humans, serum PFOA was associated with early termination of breastfeeding in a cohort of U.S. mothers (Romano et al. 2016) and PFOA, PFOS, PFNA, and PFDA serum concentrations were associated with shorter duration of breastfeeding in a cohort of mothers in the Faroe Islands (Timmermann et al. 2016). Despite the clinical significance of this endocrine disruption outcome, it is ignored in ATSDR's draft. In addition, altered mammary gland development may increase breast cancer susceptibility later in life (Rudel et al. 2011, Macon and Fenton 2013). The New Jersey DEP noted that delayed mammary gland development, along with increased liver weight, were the two most sensitive non-carcinogenic endpoints associated with PFOA exposure (NJDWQI 2017). NJDEP concluded that the target serum concentration to be protective of delayed mammary gland development was below the median serum PFOA level in the general population. While NJDEP's recommended MCL was not based on this endpoint due to a lack of precedent for using this endpoint as the basis for risk assessment, NJDEP applied an extra uncertainty factor to account for this and other sensitive endpoints.

Consideration of approaches developed by other state agencies. In addition to the ATSDR Toxicological Profile and EPA's supporting documents for the 2016 Health Advisories, NHDES should consider additional documents developed by state agencies. The State of New Jersey has adopted an MCL of 13 ng/L for PFNA (NJDWQI 2015), and the Drinking Water Quality Institute has recommended MCLs of 14 ng/L for PFOA (NJDWQI 2017) and 13 ng/L for PFOS (NJDWQI 2018, Pachkowski et al. 2018). In addition to health assessments, New Jersey has also considered availability of analytical methods and availability of treatment options (NJDEP 2018).

Some states have adopted drinking water guidelines for multiple PFAS compounds. In 2018, the Vermont Department of Health issued a health advisory of 20 ng/L for the sum of five PFAS

compounds (PFOA, PFOS, PFHxS, PFNA, PFHpA), citing their co-occurrence and similarities in chemical structure and health effects (VT DOH 2018). Massachusetts and Connecticut have established guidelines of 70 ng/L for the sum of these same five compounds (CT DPH 2016 MADEP 2018). While these comprise a small fraction of the estimated thousands of PFASs on the global market, they represent an effort to adopt a precautious approach to a broader range of compounds with similar chemical structures but far less toxicity data.

Consideration of additional PFAS compounds. ATSDR states that shorter-chain PFASs are less bioaccumulative. However, emerging research demonstrates select shorter-chain alternatives may bioaccumulate to the same extent or in excess of legacy compounds such as PFOA or PFOS (De Silva et al. 2016; Gomis et al. 2015; Liu et al. 2017; Pan et al. 2017; Shi et al. 2015). Pharmacokinetic models suggest that shorter-chain alternatives may be equally toxic compared to legacy compounds after adjusting for differences in toxicokinetics (Gomis et al. 2018). Shorter-chain alternatives replacing legacy PFASs continue to be produced and show widespread environmental occurrence. Perfluoroalkyl ether carboxylic acids (i.e. HFPO-DA or "GenX"), polyfluoroalkyl carboxylic acids, and polyfluorinated alkanesulfonates and sulfates persist in air, surface water, and drinking water downstream from release sources (Gebbink et al. 2017; Kaboré et al. 2018; Newton et al. 2017; Pan et al. 2018; Sun et al. 2016). Methods to measure extractable or adsorbable organic fluorine, based on combustion ion chromatography, can provide an indication of the total PFAS content in water samples and the proportion that is not identified by compound-specific analyses (McDonough et al. 2018).

Consideration of benefits and costs associated with establishment of MCLs. The benefits of establishing MCLs for PFAS compounds include identification of water supplies previously unknown to contain PFASs, reductions in exposures to PFASs for both compounds specified in the MCLs as well as co-occurring compounds, and prevention of adverse health outcomes associated with PFAS exposures. Since our understanding of adverse health effects evolves over time and we may become aware of toxicity at lower levels of exposure, we may underestimate the benefits of exposure reduction on the basis of our current understanding of health effects. For endocrine disrupting compounds (EDCs), an international panel of experts estimated the costs of disease and dysfunction associated with EDC exposures in the European Union to be over $200 billion (Trasande et al. 2015), and even higher costs were estimated for EDC exposures in the U.S. (Attina et al. 2016).

The costs associated with establishment of MCLs include analytical fees for routine water testing by public water supplies, water treatment for systems that are found to contain PFAS levels of concern, remediation of contaminated sites, and possible depreciation of real estate values in areas discovered to have contaminated water. NJDEP estimated costs of testing and treatment as part of the process for adopting its PFNA MCL in 2017 (NJDEP 2017).

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