August 20, 2018

Docket Number ATSDR-2015-0004
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
1600 Clifton Road, NE
Mail Stop F-57
Atlanta, GA 30329

Re: Comments on the Draft Toxicological Profile for Perfluoroalkyls, Draft for Public Comment (June 2018)

To Whom It May Concern:

The Chemical Products and Technology Division (CPTD) of the American Chemistry Council (ACC)[1] offers the enclosed comments on the June 2018 draft Toxicological Profile for Perfluoroalkyls. ACC supports the application of the best available science to understanding the potential health effects associated with exposure to per- and poly-fluoroalkyl substances and the effective communication of this information to public health officials. The latest draft of the Toxicological Profile represents a significant departure from the provisional minimum risk levels (MRLs) for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) proposed in the 2015 draft Profile. In addition, the current draft proposes MRLs for perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) for the first time and analyzes data available for a number of other perfluoroalkyl substances (PFAs).

The draft Toxicological Profile provides a comprehensive summary of the information available for the PFA substances, but includes a number of questionable assumptions used to develop the MRLs. Among our concerns are the choice of studies used to define adverse effects relevant to humans, the methods used to predict exposures in humans, and the use of uncertainty factors in the evaluation of risk. We urge ATSDR to reconsider these assumptions. Furthermore, because of the significance of the draft Toxicological Profile to the consideration

[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. ACC's Chemical Products and Technology Division is composed of a wide range of more than 60 self-funded product and sector groups that are focused on specific chemistries and related technologies. Members participating in these groups include large and small manufacturers, formulators, downstream users, distributors, suppliers and other trade associations.

of the four specific substances and of future PFAs and related substances, it is critical that ATSDR conduct a formal peer review of the document prior to its finalization.

ATSDR notes that MRLs are "intended to serve as screening levels" and are not intended to serve as standards. Unfortunately, these values are often misunderstood by the public which can cause significant confusion and alarm. It is vitally important that, for high-profile substances like PFAs, ATSDR make every effort to ensure that the Toxicological Profiles reflect the best science and avoid the temptation to be overly conservative.

Please feel free to contact me at srisotto@americanchemistry.com or at (202) 249-6727 if you any questions on the enclosed information.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director
Chemical Products and Technology Division

Enclosure

cc: W. Cibulas, Environmental Toxicology Branch

American Chemistry Council
Chemical Products and Technology Division
Comments on the

Agency for Toxic Substances and Disease Registry
Draft Toxicological Profile for Perfluoroalkyls
(June 2018)

I. Executive Summary

In its latest draft of the Toxicological Profile for Perfluoroalkyls, the Agency for Toxic Substances and Disease Registry (ATSDR) incorporates a number of questionable scientific approaches in deriving provisional intermediate, oral minimum risk levels (MRLs) for four perfluoroalkyls (PFA) substances – perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA). For all four PFAs, ATSDR bases the MRL derivation on developmental or thyroid effects in rodents while noting that there is "strong evidence" that these effects involve a pathway that is of questionable relevance to humans. In the case of PFOA and PFOS, more relevant data from non-human primates exist that were the basis for ATSDR's 2015 MRL proposals. While the Toxicological Profile suggests that ATSDR conducted a weight-evidence evaluation of the epidemiological literature, only an extensive table summary of epidemiology studies appears to be available for comment and the epidemiology studies play only a minor role in the derivation of the proposed MRLs.

The methodology ATSDR does not account for non-linear toxicokinetics indicated by available pharmacokinetic modeling and significantly overstates the persistence of three of the substances in humans. In developing three proposed MRLs, ATSDR includes an additional modifying factor of 10 for database deficiencies in a manner that is not consistent with Environmental Protection Agency (EPA) guidance on the application of database uncertainty. The draft Toxicological Profile also incorrectly characterizes the proposed MRLs as intermediate values when they are based on an assumption of chronic ($\geq$365 days), not intermediate, exposure in humans.

As a result of numerous questionable and flawed assumptions, the MRLs proposed in the 2018 Toxicological Profile exhibit unprecedented levels of conservatism that directly contradict ATSDR's previous conclusions about these substances and differ considerably with the conclusions of other regulatory authorities including Health Canada[1] and an expert panel convened by the Australian Department of Health.[2] The draft findings are inconsistent with available information on the mechanisms of toxicity and exposure on which the proposed levels

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[1] Citations provided later in this report.

[2] Expert Health Panel for Per and Poly-Fluoroalkyl Substances (PFAS). Available at www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-expert-panel.htm

are based. The draft Profile should be withdrawn and subject to a formal peer review, conducted by independent toxicologists and risk assessors, prior to the release of a subsequent draft Profile that addresses the multiple concerns outlined in this comment.

II. Introduction

PFA substances have been in widespread use for many years because of their stability, their ability to impart water and oil repellency, and unique fire-fighting abilities. The two most common PFAs – PFOA and PFOS – are no longer manufactured in the United States, Japan, and Europe in response to concerns about their environmental persistence and potential toxicity. They have been replaced with other per- and poly-fluoroalkyl substances that have improved toxicity and environmental profiles. Although biomonitoring data collected in the late 1990s and early 2000s suggested that levels of PFOA and PFOS were accumulating in humans, data collected by the Center for Disease Control and Prevention (CDC) as part of the National Health and Nutrition Exposure Surveys (NHANES) show a drop of 60 to 80 percent since that time, as a result of the phase out of the production and use of these substances.[3] Despite the past widespread use of PFOA and PFOS, the data from EPA's third Unregulated Contaminant Monitoring Rule (UCMR 3) indicate that the substances were detected in only 2 percent of the nearly 6,000 public water systems (PWS) sampled. PFHxS and PFNA were detected in less than 2 percent of the wells.

ATSDR's June 2018 document is the third draft Toxicological Profile for PFAs. The original draft was released in May 2009; a subsequent draft was issued in August 2015. Like the current version, the 2015 draft reviewed the available literature for all of the PFAs for which monitoring data were available. The 2015 draft, however, only proposed MRLs for PFOA and PFOS since ATSDR concluded that the data on the other substances were insufficient to establish values. The current Profile updates the scientific literature for the PFAs, but largely depends on studies available for the previous draft for the MRL derivation. In developing the current MRLs, however, ATSDR appears to reverse its previous conclusion that rodent data are not appropriate for calculating human health toxicity values based on equivocal data suggesting that developmental effects in rodents may be more relevant than previously thought.

The draft Toxicological Profile represents a comprehensive review of the available information on the 14 PFAs identified in the NHANES or other monitoring studies. Although we have not conducted an extensive review of the available literature, we have identified several key publications that were not considered by ATSDR, however. In addition, the draft does not fully consider the conclusions of some of the referenced studies regarding important aspects of its analysis. Failure to include this information significantly impacts ATSDR's findings.

ATSDR's toxicological profiles, and the MRLs contained within, are used extensively by local public health officials to address community concerns and to assess the need to protect public

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[3] Olsen GW *et al.* Per and polyfluoralkyl substances (PFAS) in American Red Cross adult blood donors, 2000-2015. *Environ Res* 157:87-95 (2017).

health. It is important that MRLs are determined to be health protective, but it is equally important that they be firmly grounded in science and subject to rigorous review. Although ATSDR clearly cautions that its MRLs are screening tools for hazardous waste sites and are not intended to define clean-up or action levels, the Agency must recognize that the MRLS often serve as the primary basis for assessing potential health impacts. This is particularly true for PFAs for which considerable confusion exists regarding the most scientifically robust and approach to developing health protective values.

III. Principal Study Selection

Many of the effects observed in the rodent studies, particularly liver and developmental effects, involve the activation of the peroxisome proliferator activated receptor (PPARα) or other nuclear receptors. Activation of the PPARα receptor in rodents initiates a characteristic sequence of morphological and biochemical events, principally, but not exclusively, in the liver (Kennedy *et al.* 2004).[4] The proliferation of peroxisomes has been associated with a variety of effects, including hepatocellular hypertrophy, alterations in lipid metabolism, and decreased pup survival and immune effects. Since humans and non-human primates have been found to be less responsive to PPARα agonists than rodents (Corton *et al.* 2014),[5] the relevance of the rodent findings to humans has been questioned. As a result, ATSDR concluded in its 2015 draft Toxicological Profile that "derivation of MRLs based on rodent data may result in overly conservative values" and instead based the proposed MRLs on studies in non-human primates which ATSDR noted "may be a suitable model for human exposure to PFOA and PFOS."[6]

Both the 2015 and current drafts of the Toxicological Profile describe the available evidence suggesting that PFAs may exert some adverse effects in rodents through mechanisms other than activation of PPARα. Although the current draft provides a minimal amount of new evidence for PPARα-independent mechanisms, ATSDR has apparently concluded that the data are now inexplicably sufficient to reverse its previous conclusion relative to the use of rodent data. As a result, three of the four proposed MRLs are based on developmental effects in rodents. For both PFOA and PFOS, for example, the proposed MRLs are based on a study that ATSDR previously decided not to use. For PFHxS and PFNA, moreover, ATSDR's conclusions ignore evidence that the rodent data used to derive the MRLs may not be relevant to humans.

The approach taken by ATSDR in the draft Toxicological Profile is not consistent with current recent best practices and scientific guidance on systematic review.[7] ATSDR provides a simple

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[4] Kennedy GL *et al.* The toxicology of perfluorooctanoate. *Crit Rev Toxicol* 34(4):351-384 (2004).

[5] Corton JC *et al.* Mode of action framework analysis for receptor-mediated toxicity: the peroxisome proliferator-activated receptor alpha (PPARα) as a case study. *Crit Rev Toxicol* 44(1):1–49 (2014).

[6] ATSDR. Draft toxicological profile for perfluoroalkyls. Department of Health and Human Services, Atlanta, GA (August 2015), at 32. (ATSDR 2015)

[7] National Toxicology Program. OHAT Risk of Bias Tool for Human and Animal Studies. Office of Health Assessment and Translation. Research Triangle Park, NC: Division of the National Toxicology Program, National

review of its literature review framework (Appendix B) – rather than an assessment of the risk of bias, key features, and data confidence of the available studies that are a part of accepted systematic review practices and that are included in other recent Toxicological Profiles.[8] Given the heightened public interest in PFAs and related substances, it is perplexing that ATSDR would not feel compelled to "show its work" in assessing the available studies.

a. PFOA

The proposed MRL is based on reports of altered activity and skeletal effects in the adult offspring of mice exposed to PFOA through gestation. Both studies include a single-dose group which greatly limits their value as critical studies for evaluating low doses because of the absence of a dose-response relationship. In the study by Onishchenko *et al.* (2011), mild sex-related differences in exploratory behavior patterns were reported after 5 weeks of age. PFOA-exposed males were more active, while PFOA-exposed females were less active, than their respective controls.

In the second principal study identified by ATSDR, Koskela *et al.* (2016) reported mild alterations in bone morphometry and mineral density of femurs and tibias in mice while noting that the biomechanical properties of the bones were not affected. Based on the absence of an impact on mechanical function, the biological significance of bone geometry and mineral density alterations is uncertain and may not be a suitable basis for the MRL calculation. Notably, no increases in the occurrence of malformations/variations were observed in similar studies conducted in rats.[9,10] Koskela *et al.* also appear to have conducted their statistical analysis on a per-fetus basis, rather than per-litter as advised by EPA's guidelines for assessing developmental toxicity which has been widely critiqued as a study deficiency in the past.[11] If ATSDR were to conduct the expanded systematic review tables and weigh the strengths and weaknesses of candidate primary studies alongside one another in the Appendix B tables requested in the section above, this would become readily apparent.

Lau *et al.* (2006) also reported skeletal effects in the offspring of mice exposed to PFOA, but the effects did not increase in a dose-related manner. Consequently, the effects noted by Lau *et al.*

Institute of Environmental Health Sciences (2015). https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html.

[8] ATSDR. Draft toxicological profile for molybdenum. Department of Health and Human Services, Atlanta, GA (April 2017).

[9] Staples *et al.* The embryo-fetal toxicity and teratogenic potential of ammonium perfluorooctanoate (APFO) in the rat. *Fundam Appl Toxicol* 4(3 Pt 1): 429–440 (1984).

[10] Butenhoff *et al.* The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicol* 196(1–2):95–116 (2004).

[11] EPA. Guidelines for developmental toxicity risk assessment. Risk Assessment Forum. EPA/600/FR-91/001(December 1991). (EPA Guidelines 1991). https://www.epa.gov/risk/guidelines-developmental-toxicity-risk-assessment

would generally not be considered biological significant.[12] In noting the striking difference between their results and the minor effects reported in the two-generation study in rats by Butenhoff *et al.* (2004), the authors suggest that they are most likely related to pharmacokinetic differences between the two species.

In its 2015 assessment of PFOA, ATSDR chose the increase in liver weights in *Cynomolgus* monkeys reported by Butenhoff *et al.* (2002) as the basis for its proposed MRLs. In the current assessment, ATSDR concludes that the small number of animals examined in the Butenhoff *et al.* study and the early deaths at several dose levels preclude using the non-human primate data for the MRL calculation. Given that the effects seen in the non-human primates are consistent with those reported by Butenhoff *et al.* (2012) in rats, and that there is evidence of histological hepatic effects in rats coupled with increased liver weight and hypertrophy that provide an indication that the effects are adverse – rather than adaptive[13] – it may be appropriate to use evidence of adverse histotological effects in the rat liver as the basis for the MRL.[14]

b. PFOS

The current draft of the Toxicological Profile proposes an MRL for PFOS based on a two-generation study by Luebker *et al.* (2005) reporting delayed eye opening and decreased pup weight in rats. These effects appear to occur independent of PPARα activation and, consequently, should be considered relevant to humans. In its MRL derivation, however, ATSDR has ignored the conclusions of the authors regarding the relevant dose resulting in the adverse effects.

In the case of pup weight, the decreases noted in the second generation (F2) offspring at 0.4 milligrams per kilogram body weight per day (mg/kg) were transient, disappearing by the end of lactation. Reduced body weights were not reported in the F1 pups from the 0.4 mg/kg dose group. For both F1 and F2 offspring, body weight was reduced in the 1.6 mg/kg group. As a result the authors identified 0.4 mg/kg as a no-observed-adverse-effect level (NOAEL) and 1.6 mg/kg as a lowest-observable-adverse-effect level (LOAEL). ATSDR, in contrast, inappropriately considers the LOAEL to be 0.4 mg/kg without explanation.

Similarly Luebker *et al.* conclude that the slight delay in eye opening observed in the F1 pups from the 0.4 mg/kg dose group should not be considered an adverse effect, and identify 0.4

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[12] EPA Guidelines 1991, at 13. The 1991 guidelines note that a dose-related increase in variations in skeletal ossification is interpreted as an adverse developmental effect, but assessing the biological significance of the variation must take into account what is known about the developmental stage.

[13] Hall AP *et al.* Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP Expert Workshop. *Toxicol Pathol* 40(7): 971–994 (2012).

[14] Health Canada. Perfluorooctanoic acid (PFOA) in drinking water. Document for public consultation (2016a). https://www.canada.ca/en/health-canada/programs/consultation-perfluorooctanoic-acid-pfoa-in-drinking-water/document.html

mg/kg as the NOAEL. This finding is consistent with the results from the other studies in rats and mice referenced in the draft Profile which report NOAELs of 1.0 mg/kg or more.

ATSDR's decision to consider 0.4 mg/kg as a LOAEL, rather than NOAEL, has a significant impact on the MRL calculation. Correcting the calculation to consider 0.4 mg/kg as a NOAEL makes the MRL calculation more consistent with the "intermediate" oral PFOS MRL proposed in the 2015 draft Toxicological Profile which was based on non-human primate data.

c. PFHxS

Very few studies exist that could be used as a basis for calculating an MRL for PFHxS. As noted in the draft Profile, the hypertrophy and other hepatic effects reported by Butenhoff *et al.* (2009) and Bijland *et al.* (2013) are not considered relevant for human risk assessment, based on the criteria described by Hall *et al.* Although Butenhoff *et al.* also report thyroid follicular cell damage, they note that that the observed changes in rats "are consistent with the known effects of inducers of microsomal enzymes where the hepatocellular hypertrophy results in a compensatory hypertrophy and hyperplasia of the thyroid." Because of the possible link to PPARα activation in the liver and the significant differences in thyroid function between rodents and humans,[15] the rat data are not appropriate for use in human risk assessment.

Based on the strong likelihood that both the available hepatic and thyroid effects data from animal studies are not relevant to humans, ATSDR should withdraw its proposed MRL for PFHxS.

d. PFNA

ATSDR identifies only three animal studies available for in the draft Toxicological Profile. Significantly, one of these studies (Wolf *et al.* 2010) reported that the developmental effects in offspring of mice exposed to PFNA required PPARα activation that is of questionable relevance to humans.[16] The decreased body weight gain and development delays reported in the offspring of mice administered PFNA via gavage on GDs 1-17 in Das *et al.* 2015 occurred concomitant with maternal toxicity and therefore, should not be used as the critical effect. Moreover, Wolf et al. (2010) in PPARα knockout mice did not find alterations in pup body weight or postnatal development at 2 mg/kg-day, suggesting that these effects are rodent-specific responses to PFNA. Since developmental concerns were also not identified from the PFNA epidemiology literature, it is not clear what rational ATSDR would have to conclude that the decreased pup body weight and developmental delays from Das *et al.* are appropriate endpoints for evaluating human health risk from exposure to PFNA.

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[15] Capen CC *et al.* Species differences in thyroid, kidney, and urinary bladder carcinogenesis. *IARC Scientific Publications* 147:1-14 (1999).

[16] Although the authors did not rule out the possibility of PPARα relevance to a human response to PFNA, they noted the lower number of these receptors in the liver of humans versus mice.

As is the case for PFHxS, the available data do not support the development of an MRL for PFNA.

IV. Available Epidemiology

A number of epidemiology studies have evaluated potential health outcomes associated with occupational, drinking water, and population exposures to PFAs, particularly PFOA and PFOS. Most of the studies lack exposure monitoring data; most provide only a single measurement which does not provide information on historical exposure. The lack of historical exposure data is a particular limitation of the occupational and community population studies where past exposures were typically higher than current exposures. Although several studies have reported statistically significant associations, the findings are not consistent across studies. Observed dose-response patterns in some studies are also less clear when evaluated across multiple studies. Using a weight-of-evidence approach, the draft Toxicological Profile identifies several potential hazard associated with PFA exposure.[17] The details of the WOE analysis of the epidemiology studies should be made available to the peer reviewers and the public for comment on its scientific merits.

While ATSDR suggests that its approach to developing MRLs is to identify sensitive endpoints from epidemiology studies, the human studies appear to play only a minimal role in the proposed MRLs for the PFAs. Most of the endpoints chosen as the basis for the proposed MRL from animal studies do not align with endpoints identified in the epidemiological studies. This is particularly true for PFHxS and PFNA and supports a conclusion that the data are not sufficient for developing an MRL for these two PFAs.

Notably a recent Expert Health Panel commissioned by the Australian Department of Health reviewed the epidemiology data for PFOA and PFOS and found limited or no evidence for any causal link with any human disease. [18]

V. Estimating Human Exposures

Large pharmacokinetic differences exist between humans and animals for the PFAs considered by ATSDR, with lower clearance (i.e., higher half-life values) reported for humans than for rats, mice, and non-human primates. These differences result in higher target tissue doses in humans when exposed to the same external doses as laboratory animals. Consequently, default approaches for interspecies extrapolation (e.g., using an interspecies uncertainty factor of 10 or allometric scaling) are not considered to be sufficiently predictive. To better account for these interspecies toxicokinetic differences, the World Health Organization (WHO) developed an approach using chemical-specific adjustment factors (CSAF). [19] Consistent with

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[18] www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-expert-panel.htm

[19] WHO. Chemical specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment. International Programme on Chemical Safety. World Health Organization. Geneva (2005).

this approach, ATSDR calculates a human equivalent dose (HED) for the PFAs by adjusting the serum concentration in rodents measured at the drinking water exposure by the rate of clearance (CL) of the substance from the human body in developing the proposed MRLs. The CL was calculated using the estimated volume of distribution and serum elimination half-life.[20]

Internal dose ratios predicted by the available physiologically-based pharmacokinetic (PBPK) models indicate, however, that the interspecies extrapolations for PFOA and PFOS are highly dose dependent, and result from nonlinear toxicokinetics. [21] As a result, a single interspecies extrapolation factor such as that used by ATSDR is not scientifically supportable for either PFOA or PFOS. Instead an approach that uses CSAF values derived from the PBPK models better addresses the issue of nonlinear toxicokinetics and its impact on interspecies extrapolation. Using such an approach, Health Canada compared dose metrics predicted by the various animal PBPK models to calculate a CL ratio between species (CL_A/CL_H).[22] They reasoned that using the model data to derive the CL_A/CL_H allows for a more appropriate comparison of doses of the same magnitude.[23] Using the CL ratio to estimate exposures, Health Canada's analysis indicates that the approach taken by ATSDR significantly underestimates the human clearance rate and, as a result, ATSDR calculates HED values that are 10 to 500 times lower than actual. Human biomonitoring declines reported in the last decade support this point.

As described, the risk assessment calculations by both ATSDR and Health Canada are highly dependent on the estimate of the elimination half-life in humans. Reported half-life estimates in humans range considerably and appear to show a gender differences for at least some PFAs. Estimates of the mean half-life for PFOA vary from 2.3 years in a study of a general population exposed via drinking water[24] to 3.8 years in an occupationally-exposed cohort. [25] For PFOS, a

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http://apps.who.int/iris/bitstream/handle/10665/43294/9241546786_eng.pdf;jsessionid=45918ABD3B07EF944ACD546CF50B974F?sequence=1

[20] The volume of distribution is defined as the volume of blood (in milliliters per kilogram) in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration. Half-life is a measure of the time (in days) required to eliminate one half of a quantity of a chemical from the body.

[21] Loccisano AE *et al.* Comparison and evaluation of pharmacokinetics of PFOA and PFOS in the adult rat using a physiologically based pharmacokinetic model. *Reprod Toxicol* 33(4):452–467 (2012).

[22] For each species, the PBPK model was used to predict internal doses for a broad range of oral doses. Model simulations were continued until steady-state conditions or expected lifetimes were reached (Loccisano *et al.* 2012).

[23] Health Canada 2016a; Health Canada. Perfluorooctane Sulfonate in Drinking Water. Document for public consultation. Prepared by the Federal-Provincial-Territorial Committee on Drinking Water (2016b). https://www.canada.ca/en/health-canada/programs/consultation-perfluorooctane-sulfonate-pfos-in-drinking-water/document.html

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

[25] Olsen GW *et al.* Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Persp* 115:1298–1305 (2007).

recent analysis of data from the NHANES[26] from 1999-2000 through 2013-2014 estimated a serum elimination half-life of PFOS of 3.8 years in males and 3.4 years in females. [27] Similarly, data from a community in Sweden exposed to PFAs via a contaminated water supply following installation of a treatment system suggested a serum elimination half-life for PFOS of 3.4 years for 106 residents aged 4 to 83.[28] An earlier study of occupational exposures, on the other hand, suggested a half-life of 5.4 years for PFOS among retired workers.

Although there are less data available for PFHxS, the information that exists suggests a similar pattern of a longer half-life estimate for occupational studies than for those in the general population. While the 2007 study of retired workers suggested a half-life of 7.3 to 8.5 years,[29] a recent analysis in a population exposed to contaminated drinking water suggests a half-life of 5.3 years.[30] For PFNA, ACC/CPTD is aware of only one study that estimates half-life based on analysis in urine collected from a general population sample.[31]

As ATSDR notes, human elimination half-lives estimates are most applicable to the serum levels of the study population from which they were derived, which are several orders of magnitude higher in workers compared to the general population. While the occupational estimates generate more conservative estimates, half-life values derived from general population data are the most relevant to exposures considered by ATSDR.[32] Reducing the half-life estimate from 3.8 to 2.9 years for PFOA and from 5.4 to 3.4 years for PFOS significantly affects ATSDR's estimate of human serum levels associated with exposure from drinking water. For PFOS, for example, assuming a half-life of 3.4 years increases the exposure required to achieve human serum concentrations equivalent to those in the rodent studies by a factor of 10.

VI. Application of Uncertainty and Modifying Factors

ATSDR has proposed to adjust the Human Equivalent Dose by a factor of 300 to generate the MRL for each of the PFA to account for uncertainties in the available data base. In each case, the Agency includes a factor of 3 as a dosimetric adjustment to extrapolate from animal to humans and a factor of 10 for human variability. For PFOA, ATSDR adds an additional factor of

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[26] More information on NHANES is available at https://www.cdc.gov/exposurereport/index.html.

[27] Gomis MI *et al*. Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. *Environ Int.* 108: 92-102 (2017).

[28] Li Y *et al.* Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup Environ Med.* 75:46-51 (2018). Li *et al.* 2018

[29] Olsen *et al.* 2007.

[30] Li *et al.* 2018.

[31] Zhang Y *et al.* Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. *Environ Sci Tech* 47 (18):10619-10627 (2013).

[32] EPA. Health effects support document for perfluorooctanoic acid (PFOA). EPA 822-R-16-003 (May 2016), at 4-12. https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final_508.pdf

10 to account for the use of a LOAEL, instead of a no-effect level. For the other three, a modifying factor of 10 is added for data base uncertainty, based on "concern that immunotoxicity may be a more sensitive endpoint" than the developmental/thyroid effects chosen as the basis for the MRL.

As discussed earlier, the two principal PFOA studies identified by ATSDR are single-dose studies which greatly limits their value in evaluating low doses. Both studies report only mild effects of questionable biological significance. The results of skeletal defects in mice, moreover, contradict the findings of two studies in rats. Consequently, the two principal studies represent poor choices for generating the proposed MRL and seem to be selected because they generate the lowest value, particularly with the inclusion of a 10-fold LOAEL/NOAEL adjustment. Given the significant number of available animal studies, including a non-human primate study, ATSDR should select an alternative basis for the MRL that can provide a more scientifically robust and defensible result.

The addition of a modifying factor for PFOS, PFHxS, and PFNA is equally problematic. While ATSDR provides no guidance on how to apply a modifying factor based on data base uncertainty, EPA's guidance explains that a database uncertainty factor (UF_D) is applied when reproductive and developmental toxicity studies are missing since they have been found to provide useful information for establishing the lowest no adverse effect level.[33] The EPA guidance notes that, for a reference dose (RfD) based on animal data, a factor of 3 is often applied if either a prenatal toxicity study or a two-generation reproduction study is missing, or a factor of 10 may be applied if both are missing.[34] In deciding whether to apply an UF_D, EPA advises that the assessor should consider both the data lacking and the data available for particular organ systems as well as life stages.[35] In the case of both PFHxS and PFNA, for which little data exist for any endpoint and no chemical-specific data exist to suggest immunotoxicity, it is unclear what scientific basis ATSDR uses to conclude a modifying factor is appropriate. In fact, the discussion of a modifying factor is the first time that immunotoxicity is mentioned in the draft Profile in the context of either of these two substances.

As for PFOS, the reproductive and development data base is robust and does not suggest the need to account for an incomplete characterization of toxicity. Similarly, the potential immunotoxic effects of PFOS have been studied in both laboratory animals and humans. The

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[33] Ibid, at 4-45.

[34] Dourson ML *et al.* (1996) Evolution of science-based uncertainty factors in noncancer risk assessment. *Regul Toxicol Pharmacol* 24:108–120 (1996).

[35] EPA Risk Assessment Forum. A review of the reference dose and reference concentration processes. EPA/630/P-02/002F (December 2002). https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf

results of these studies are inconsistent and both EPA[36] and Health Canada[37] have questioned the relevance of immune system effects observed in mice and the small antibody variations seen in epidemiology studies to adverse health effects in humans. It is inappropriate, therefore, to conclude that immunotoxic effects represent a more sensitive health effect such that a modifying factor of 10 should be included.

VI. Exposure Duration

ATSDR's characterization of the proposed MRLs as intermediate (15 to 364 days) is inconsistent with their derivation, as outlined above. While the levels are based on data collected in non-chronic studies, the dosimetric modeling is based on serum levels in humans reaching steady-state.[38] Based on pharmacokinetic modeling, the time to reach steady state in human serum for PFOA and PFOS requires more than 364 days.[39] This is likely to also be true for PFHxS and PFNA with estimated half-lives of 3,100 and 900 days, respectively. Consequently, the proposed MRLs are based on an assumption of chronic (≥365 days), not intermediate, exposure in humans.

VIII. Impact on MRL Calculation

The above comments outline several assumptions in the ATSDR analysis that significantly impact the derivation of the proposed MRLs.[40] Based on our analysis, these assumptions add a level of conservatism of 1000-fold or more to the proposed MRLs for PFOA and PFOS – assuming no change in the principal studies. The proposed MRL for PFOA-oral, intermediate is 10,000 times lower than the point of departure (POD) based on the LOAEL for mice and 100,000 times lower than the POD for non-human primates. This seems inappropriate given that rodents are more sensitive to PFOA than humans in terms of PPAR-mediated responses, and thus are not quite representative of humans.

Given the significant number of questionable assumptions that ATSDR has made, and the impact of these assumptions on the proposed MRLs, it is vitally important that the approach taken in the draft Toxicological Profile be reevaluated and that the draft be subject to formal peer review before the MRLs are used in any fashion.

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36 EPA. Health effects support document for perfluorooctane sulfonate (PFOS). EPA 822-R-16-002 (May 2016). https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf

37 Health Canada 2016b.

38 Wambaugh *et al.* Dosimetric anchoring of *in vivo* and *in vitro* studies for perfluorooctanoate and perfluorooctanesulfonate. *Toxicol Sci* 136(2):308-327 (2013).

39 Loccisano *et al.* 2012.

40 Given the multi-step derivation of the proposed MRLs, including the application of prediction models, a quantitative uncertainty analysis should be performed. The results of this analysis should be presented with the proposed MRLs to ensure accurate, science-based risk communication.