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Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
1600 Clifton Rd. NE., F57
Atlanta, GA 30329–4027

Re: Comments on the June 23, 2018 draft *Toxicological Profile for Perfluoroalkyls*

Dear Colleagues:

We write to provide comments to the Agency for Toxic Substances and Disease Registry (ATSDR) on its proposed Minimum Risk Levels (MRLs) for perfluoroalkyl substances (PFAS). We recognize that the Agency has put considerable effort into generating these values, and hope that our criticisms will be helpful to the Agency as it finalizes its Toxicological Profile for PFAS. It should be our collective goal that stakeholders and regulators continue to thoroughly examine the best available scientific information when proposing risk-based levels for PFAS compounds.

As a general matter, we suggest that the Agency consider coordinating its efforts with the U.S. Environmental Protection Agency (EPA) to provide uniform leadership. Although ATSDR notes that its MRLs are not intended to be used as a basis of regulation, inevitably, at least at the level of many of the 50 states, they may be, either directly or through influence.

To date, toxicity values for PFAS published or proposed by EPA, ATSDR, and various states have, appropriately, erred on the side of health-protection in the face of uncertainty. However, emerging and accumulating scientific evidence can, and should, be used to further refine estimates of MRLs, reference doses (RfDs), and guidelines and standards on which these may be based. In what follows, we highlight some of this evidence, and suggest means of using it.

We agree that public health must be protected, but we are concerned that the current process for PFAS is relying too heavily on the precautionary principle to protect against uncertainty. There is a significant downside risk to this approach as implementation of protections greater than necessary will impose an expensive burden and unintended ripple effect on society in terms of drinking water treatment, additional requirements for solids and liquids waste management and reuse, and remediation. In addition to the potential financial burden, overprotection will also add to unwarranted stress, fear and concern of the general public who have been (or are being) exposed to PFAS in drinking water. We respectfully ask that ATSDR apply sound judgment in choosing the most reliable studies to ensure its MRLs are sufficiently low to protect public health but are not overprotective and, therefore, result in a nationwide diversion of resources from addressing other contaminants with more robust demonstration of toxic effects that present greater risks to public health.

ATSDR should collaborate with EPA to establish uniform toxicity values for PFAS

A perceived lack of federal leadership in addressing PFAS has forced states to make their own decisions regarding toxicity data in order to respond to mounting public and political pressures. Toxicologists and public health officials can, and do, interpret data differently, and such differences have been reflected in state actions in establishing PFAS drinking water and groundwater standards/guidelines. Of course, there are several uncertainties associated with PFAS toxicity that provide substantial room for interpretation and disagreement. To provide greater uniformity, consistency, and regulatory authority, we like many are encouraging EPA to issue federal Maximum Contaminant Levels (MCLs), and EPA promised to consider this route of action at its May 22-23, 2018 PFAS Summit and elsewhere.[1] Even if EPA were to act, however, establishing MCLs for PFAS would require several years, and states have and will continue to feel pressured to make decisions at present regarding acceptable PFAS levels in drinking water. In addition, the general public is demanding such decisions.

It thus behooves the federal government, as represented by both ATSDR and EPA, to issue and update toxicity values (in the form of MRLs and/or reference doses, RfDs) in a timely and consistent manner for use in human health risk assessments and public health evaluations. It is not as useful, however, for ATSDR and EPA to issue differing values, as the lack of uniformity serves to confound the present problem of states issuing independent and conflicting values.

Differing approaches between ATSDR and EPA also reduces the confidence of state regulators and the general public, providing further pressure to lower regulatory standards/guidelines without a scientific process. Thus, we recommend and encourage ATSDR to collaborate with EPA – perhaps through the formation of an inter-agency PFAS workgroup – to develop consensus-based values for PFAS MRLs/RfDs. Such a workgroup should meet periodically to discuss new and emerging studies to determine if toxicity values should be updated or expanded to cover more PFAS compounds. Further, such a collaborative effort by the two agencies would bring more confidence to the general public, especially those affected by PFAS detected in their drinking water, air, backyard gardens, and the like.

Several states, including Massachusetts, Connecticut, and Vermont, have decided to group five PFAS compounds (PFOA, PFOS, PFHxS, PFHpA, and PFNA) together based on their determination and assumption of similar modes of toxicity and pharmacokinetic behavior. ATSDR (ideally with EPA's cooperation) should consider whether this approach makes more sense than issuing MRLs on a compound by compound basis, and/or whether it might be possible to develop a toxicity equivalency factor scheme for PFAS compounds, similar to those used in risk assessment practice for polycyclic aromatic hydrocarbons (PAHs) and polychlorinated dibenzo(p)dioxins and furans (PCDD/Fs).

[1] See https://www.epa.gov/newsreleases/historic-epa-summit-provides-active-engagement-and-actions-address-pfas

ATSDR should develop robust toxicity values that are both evidence-based and health-protective

Paraphrasing comments made by Dr. William Savonis at the recent regional PFAS listening session hosted by EPA in Exeter, NH (June 25-26, 2018), MRLs are set at levels designed to be safe, such that there is no anticipated chance of adverse effects at levels of exposure lower than MRLs. Even at levels that modestly exceed the MRLs, there is likely no significant risk of adverse effects. We find that emerging toxicologic evidence indicates that the PFAS MRLs proposed by ATSDR are overly restrictive, such that higher values would also be protective of public health with an ample margin of safety.

Developmental health effects, based on the findings of specific toxicity studies in laboratory animals, serve as the basis of three of ATSDR's proposed PFAS MRLs. One reason that supports our contention that the proposed MRLs for PFOA, PFOS and PFNA are more protective than necessary is because the C8 Panel studies -- arguably the most extensive epidemiological investigations of PFAS health effects in humans involving the highest levels of exposure – failed to observe any associations between exposure to these compounds and adverse developmental health effects. The C8 Panel studies examined potential links between PFOA exposure and four developmental health endpoints and found no statistically significant associations. Quoting from the C8 Science Panel website (http://www.c8sciencepanel.org/prob_link.html):

- "On the basis of epidemiologic and other data available to the C8 Science Panel, we conclude that there is a not probable link between exposure to C8 (also known as PFOA) and neurodevelopmental disorders in children, including attention deficit disorders and learning disabilities."

- "On the basis of epidemiologic studies and other scientific data available to the C8 Science Panel, the conclusion is that there is not a probable link between exposure to PFOA (C8) and birth defects."

- "On the basis of epidemiologic and other scientific data available to the C8 Science Panel, the conclusion is that there is not a probable link between exposure to PFOA (C8) and miscarriage or stillbirth." and

- "On the basis of epidemiologic and other scientific data available to the C8 Science Panel, the conclusion is that there is not a probable link between exposure to PFOA (C8) and preterm birth or low birth weight."

ATSDR states (p. 25) that "Evidence is suggestive of a link between serum PFOA and PFOS and small decreases in birth weight." The overall epidemiological evidence in the report, however, does not indicate a clear relationship between PFOA and PFOS exposure and low birth weight. Figures 2-33 (PFOA) and 2-35 (PFOS) summarize the studies reviewed by ATSDR. For PFOA (Figure 2-33), the frequency of odds ratios less than one (11 instances) is greater than the number of odds ratios greater than one (8 instances), indicating no apparent relationship at all. For PFOS (Figure 2-35), the odds ratios are consistently greater than one,

but only two of the eleven groupings are statistically significant with respect to the 95% confidence interval. Perhaps the overall epidemiological evidence might be better stated as *possibly suggestive* of a link between low birth weight and serum PFOS, but not serum PFOA.

The more important question is whether slightly lower birth weights in some, though not all, studies should serve as the basis of these provisional MRLs. ATSDR itself notes (p. 517) that "decreases in birth weight were small and not likely biological (*sic*) relevant" and that "no increases in the risk of low birth weight were found in highly exposed populations." As such, there is no evidence of an adverse health effect, and use of low birth weight or other developmental effects as the bases for MRLs are ineffectually (at best) supported by epidemiological data.[2]

Moreover, the developmental findings in the laboratory rodent studies used to derive proposed MRLs for PFOS and PFNA are based on subtle, transient effects that may not be a reliable basis for toxicity values. For PFOS, the Luebker et al. (2005) study used as the basis of ATSDR's proposed MRL observed delayed eye opening and decreased pup weight in baby rats. The Leubker et al. (2005) study *itself* discounts these observations as themselves being insignificant or non-adverse effects. Quoting from the paper's discussion:

- "The slight delay in eye opening (0.6 days compared to control) in the 0.4 mg/(kg day) dose group was not considered an adverse outcome" and
- "Only transient reductions in body weights occurred during mid-lactation in the F2 generation pups at the 0.4 mg/(kg day) dose level. This observation was not considered toxicologically significant because the small reductions in pup body weights were associated with minimally larger live litter sizes at birth and on LD 4 pre-culling, as compared with the control group, and body weights in this dose group were comparable to controls at the end of lactation."

Additionally, the proposed MRL for PFOS incorporates a modifying factor of 10 to account for potential concerns over immunotoxic effects. This factor makes no sense as it is irrelevant to the chosen toxicity study and it should be dropped if ATSDR maintains the basis of the MRL on the Luebker *et al*. study (2005). Alternatively, ATSDR should change the basis of its MRL to a study based on immunotoxicity. Attempting to compensate for other health effects within an MRL based on a study that does not measure those effects is not standard practice in deriving toxicity values, certainly not when those effects have been experimentally measured (as extensively detailed in the *Toxicological Profile*).

In the case of PFOA, the Onishchenko *et al*. (2011) and Koskela *et al.* (2016) studies selected by ATSDR to be the basis of the proposed MRL are categorized by ATSDR as "less serious." health effects in Table 2-3. Given the small number of animals tested in these studies, ATSDR

[2] On a related topic, ATSDR makes the observation several times (p. 6, p. 25, and p. A-4) that any decrease in birth weight is at most small (<20 g or 0.7 ounces per 1 ng/mL). Given the weakness and uncertainty in the link between serum PFOA and PFOS and low birth weight (especially for PFOA), ATSDR should specify the certainty of this relationship, and should provide within the toxicity profile (possibly adding an Appendix) the detail on the specific source of this statement or the analysis used to derive the quantitative relationship.

should more carefully review these studies to judge whether the findings are sufficiently robust to support the derivation of an MRL.

Modifying factors of 10 are also incorporated into the derivations of the proposed MRLs for PFHxS and PFNA, two PFAS that have received less study than the C8 compounds PFOS and PFOA. While it is true that fewer studies are available, many toxicologists suspect similar behavior and modes of action among these compounds, and as previously mentioned. some states (CT, MA, and VT) have grouped these chemicals together. As such, the additional modifying factor of 10 should be eliminated, as it is unnecessary, and certainly not evidence-based. At a minimum, if it is retained, the precise value of 10, as opposed to say, *e.g.*, 3, should be justified.

Finally, all of ATSDR's proposed MRLs contain an interspecies safety factor of 3 to account for the possibility that humans may be more sensitive to PFAS than rodents (laboratory animals). As recognized by ATSDR (p. 4) and the relevant scientific community at large, humans are less responsive to activation of the peroxisome proliferator-activated receptor-α (PPARα) believed to influence many aspects (including the aspects chosen for the MRLs) of PFAS toxicity. Consequently, evidence-based interspecies "uncertainty factors" between, say, mice and human or rats and humans are actually less than 1. Health risk assessors routinely apply "chemical-specific adjustment factors" to account for these differences. ATSDR should follow suit.

In summary, when selecting the studies to serve as the bases of MRLs, ATSDR should more carefully assess the significance and relevance of the specific, laboratory rodent-based endpoints on which it relies for purposes of estimating its MRLs. We do appreciate that toxicologists differ in their judgments and opinions with regard to the evidence at hand. Nonetheless, given the inevitability of unintended consequences, choosing the most restrictive values for MRLs (which inevitably translate into guidelines and standards for drinking water, groundwater, ambient air, and so on) may not be necessary to protect public health.

ATSDR should develop current background exposure estimates for PFAS

ATSDR should use the empirical information gathered in its draft Toxicological Profile to estimate current background exposure rates to PFAS to the general public. Although not directly pertinent to the derivation of MRLs, background exposure rates to the general population are very important to regulatory agencies, such as EPA, that account for background exposure in setting drinking water guidelines such as health advisory levels and maximum contaminant levels.

For example, as part of the derivation of its 70 ng/l (ppt) LHA for PFOA and PFOS, EPA's default assumption of 80% (of the safe level of exposure) for background exposure allows drinking water to provide only a 20% relative source contribution to PFAS exposure. ATSDR discusses the Trudel *et al.* (2008) study that proposed food and water ingestion, dust ingestion, and hand-to-mouth transfer from mill-treated carpets as major exposure pathways, but the estimated exposure rates are based on numerous assumptions and older

data. The similar and more recent Gebbink *et al*. (2015) study, which we recommend that ATSDR review and incorporate into its toxicity profile, suggests that typical background exposures to PFOA and PFOS are *only about 3%,* and not 80%, of EPA's assumed safe level of exposure of 20 ng/kg-d. If EPA had adopted, say, a 90% relative source contribution for drinking water, then its derived PFOS+PFOA LHA would have been 290 ng/l, and not 70 ng/l. The significance of this one change alone cannot be overstated.

Both the Trudel *et al.* (2008) and Gebbink *et al.* (2015) studies are based on postulated exposure pathways that cannot practically be confirmed. However, population-based biomonitoring data collected since 1999 by ATSDR *can* be used to gauge overall PFAS exposure rates. Empirical data and exposure parameters described in Chapter 5 and Appendix A of the draft Toxicological Profile can be used to estimate background exposure. ATSDR provides a framework for estimating background exposure to PFAS based on the observation that concentrations of many PFAS have been decreasing in blood in the general U.S. population.[3] Such estimates may be compared with the earlier values cited from the literature in Chapter 5. Heuristically:

Rate change in PFAS body burden = Background Intake of PFAS – PFAS excretion

Adapting the nomenclature in Appendix A of the ATSDR Toxicological Profile, and assuming (as does ATSDR) 100% absorption of PFAS intake exposure:

$$\frac{d}{dt}(C_b V_d) = D_{back} - k_e C_b V_d$$

$$k_e = \frac{\ln(2)}{t_{1/2}}$$

where the terms are:

C_b	Arithmetic average concentration of PFAS in serum (blood) (ng/l);
V_d	Apparent volume of PFAS distribution (l/kg);
D_{back}	Background exposure to PFAS (ng/kg-d);
k_e	PFAS elimination constant (d^{-1}); and
$t_{1/2}$	PFAS half-life in the body (d).

PFAS concentrations have been measured in blood in the general U.S. population over several periods as part of the National Health and Nutrition Examination Survey (NHANES), the earliest in 1999, and the latest in 2013 (https://www.atsdr.cdc.gov/pfas/pfas-blood-testing.html). Assuming (1) PFAS concentrations in blood of C_{b1999} and C_{b2013} in the earliest and latest periods, (2) independence between the variables C_b and V_d, and (3) constant

[3] The fact that serum levels of many PFAS are decreasing in the general U.S. population is an important point worthy of greater emphasis in the face of growing concerns over adverse health effects. We recommend the incorporation of graphics similar to Figure 1 and Figure 2 within the ATSDR report, along with additional discussion of the declining trends.

background exposure to PFAS over the period of exposure (T = 14 yrs = 5133.5 d),[4] the differential equation can be solved and rearranged to yield the following expression for estimating the background exposure D_{back}:

$$D_{back} = \frac{k_e V_d (C_{b2013} - C_{b1999} e^{-k_e T})}{1 - e^{-k_e T}}$$

We apply this equation to the four PFAS for which ATSDR has proposed MRLs (PFOA, PFOS, PFHxS, and PFNA). Arithmetic average serum PFAS concentrations, which are appropriate for the model, are not directly available from ATSDR in the draft toxicity profile. As such, the values of the 50th, 75th, 90th, and 95th percentile levels have been extracted from CDC (2018), curve-fit to estimate parameters for assumed log-normal distributions, and the parameters have been used to estimate arithmetic means. A spreadsheet with the calculations to estimate these values is provided as an attachment to our comments.

Applying the following parameters for PFOA:

C_{b1999}	5,625 ng/l (estimated arithmetic mean, U.S. residents, 1999-2000);
C_{b2013}	2,337 ng/l (estimated arithmetic mean, U.S. residents, 2013-2014);
V_d	0.2 l/kg (average for males and females, ATSDR Table A-4);
$t_{1/2}$	1,400 d (ATSDR Table A-4); and
T	5133.5 d (14 years)

yields a background PFOA dose estimate of 0.206 ng/kg-d.

Applying the following parameters for PFOS:

C_{b1999}	33,405 ng/l (estimated arithmetic mean, U.S. residents, 1999-2000);
C_{b2013}	6,708 ng/l (estimated arithmetic mean, U.S. residents, 2013-2014);
V_d	0.2 l/kg (average for males and females, ATSDR Table A-4);
$t_{1/2}$	2,000 d (ATSDR Table A-4); and
T	5133.5 d (14 years)

yields a background PFOS dose-estimate of 0.074 ng/kg-d.

Added together, PFOA and PFOS background exposure are predicted to be on the order of less than 0.2 ng/kg-d, or less than 1% of EPA's reference dose of 20 ng/kg-d for the sum of PFOA and PFOS.

Similar estimates can be developed for PFHxS and PFNA using the blood serum data and parameters reported by ATSDR. However, unlike PFOA and PFOS, concentrations of PFHxS

[4] The pattern of serum PFNA does not indicate a steady decline since 1999, but rather an increase from 1999 through 2009, followed by a subsequent decline. The equation to consider background is thus considered over the period from 2009 to 2013 for PFNA.

and PFNA (Figure 1) have not declined as rapidly in blood as those of PFOA and PFOS (Figure 2). In fact, from 1999 to 2009, concentrations of PFNA increased (Figure 1).

Applying the following parameters for PFHxS:

C_{b1999}	2,645 ng/l (estimated arithmetic mean, U.S. residents,1999-2000);
C_{b2013}	1,350 ng/l (estimated arithmetic mean, U.S. residents, 2013-2014);
V_d	0. 287/kg (ATSDR Table A-4);
$t_{1/2}$	3,100 d (ATSDR Table A-4); and
T	5133.5 d (14 years)

yields a background PFHxS dose estimate of 0.089 ng/kg-d.

Applying the following parameters for PFNA, but adjusting the equation to cover only the recent decay period from 2009 to 2013:

C_{b2009}	1,418 ng/l (estimated arithmetic mean, U.S. residents, 2009-2010);
C_{b2013}	801 ng/l (estimated arithmetic mean, U.S. residents, 2013-2014);
V_d	0. 2/kg (ATSDR Table A-4);
$t_{1/2}$	900 d (ATSDR Table A-4); and
T	1461 d (4 years)

yields a background PFNA dose estimate of 0.078 ng/kg-d.

A more complex analysis that considers time-varying background and other factors, or a sensitivity study could be constructed to test the variability introduced by different parameter choices. But barring extreme changes in parameter values, large differences in estimated background exposure estimates are not likely. For the four PFAS considered, the inferred background exposure rates are all relatively small fractions of the MRLs proposed by ATSDR:

- PFOA: Background/MRL = 0.206 ng/kg-d ÷ 3 ng/kg-d = 7%;
- PFOS: Background/MRL = 0.074 ng/kg-d ÷ 2 ng/kg-d = 4%;
- PFHxS: Background/MRL = 0.089 ng/kg-d ÷ 20 ng/kg-d = 0.4%; and
- PFNA: Background/MRL = 0.078 ng/kg-d ÷ 3 ng/kg-d = 3%.

These estimates of background are generally lower than typical rates found by Trudel *et al.* (2008) and Gebbink *et al.* (2015), but this is not surprising given the reliance of these studies on older data when the use/presence of these PFAS compounds was likely higher. The serum PFAS data provide an important opportunity to attempt to relate use of the various PFAS compounds in commerce with temporal trends in exposure, and ATSDR should consider expanding the interpretation of the serum PFAS data.

Conclusions

We appreciate the effort that ATSDR has devoted to assessing risks of exposure to PFAS risks. However, given the implications of its proposed MRLs in influencing state actions, we strongly request that ATSDR consider more carefully the values of the MRLs it establishes. We recommend that ATSDR collaborate with EPA in setting MRLs and RfDs at levels that protect public health with a sufficient degree of safety, based on the most reliable scientific studies available and application of chemical-specific adjustment factors that account for the broader knowledge of PFAS toxicity.

References

Gebbink WA, Berger U, and Cousins IT (2015). Estimating human exposure to PFOS isomers and PFCA homologues: The relative importance of direct and indirect (precursor) exposure. *Environment International* **74**:160-169.

Luebker DJ, Case MT, York RG, *et al.* (2005). Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. *Toxicology* **215**(1-2):126-148.

Koskela A, Finnila MA, Korkalainen M, *et al*. (2016). Effects of developmental exposure to perfluorooctanoic acid (PFOA) on long bone morphology and bone cell differentiation. *Toxicol Appl Pharmacol* **301**:14-21. 10.1016/j.taap.2016.04.002.

Onishchenko N, Fischer C, Wan Ibrahim WN, *et al.* (2011). Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. *Neurotox Res* **19(3)**:452-461.

Trudel D, Horowitz L, Wormuth M, et al. (2008). Estimating consumer exposure to PFOS and PFOA. *Risk Analysis* **28(2)**:251-269.

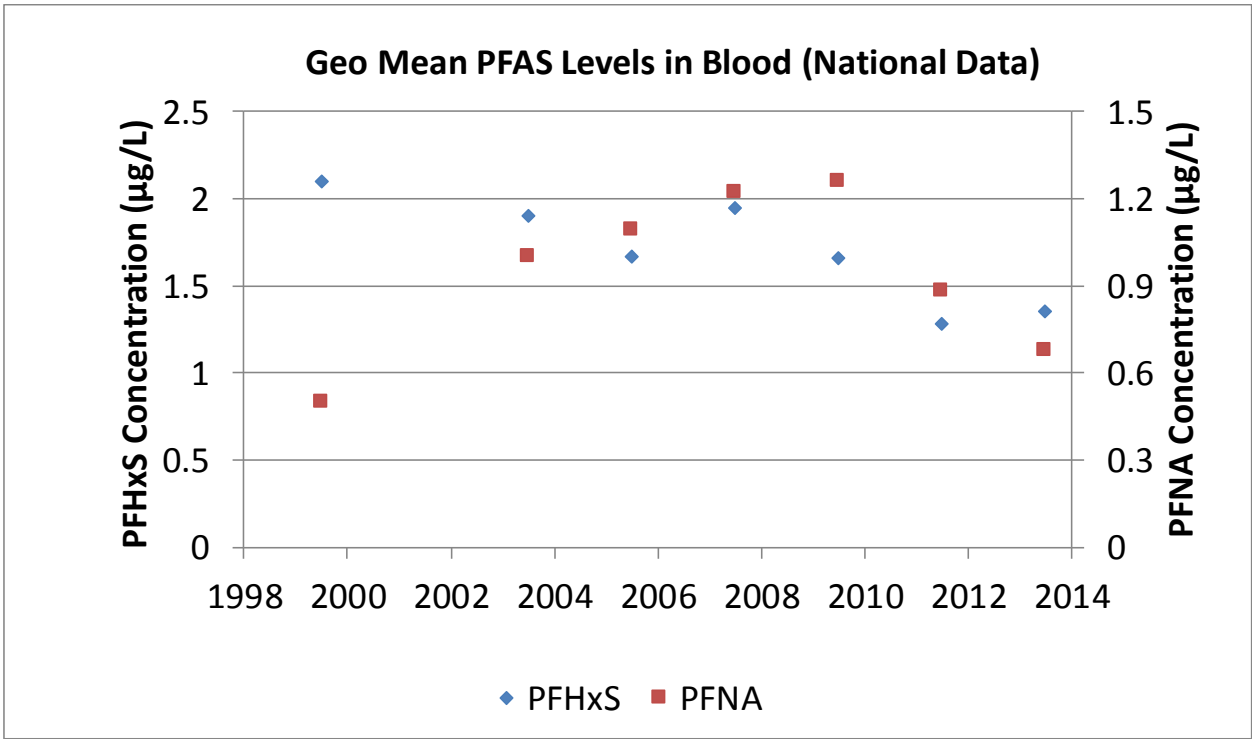

Figure 1 Geometric mean concentrations of serum PFHxS and PFNA reported for the U.S. population, from Table 5-22 of the draft ATSDR Toxicity Profiles

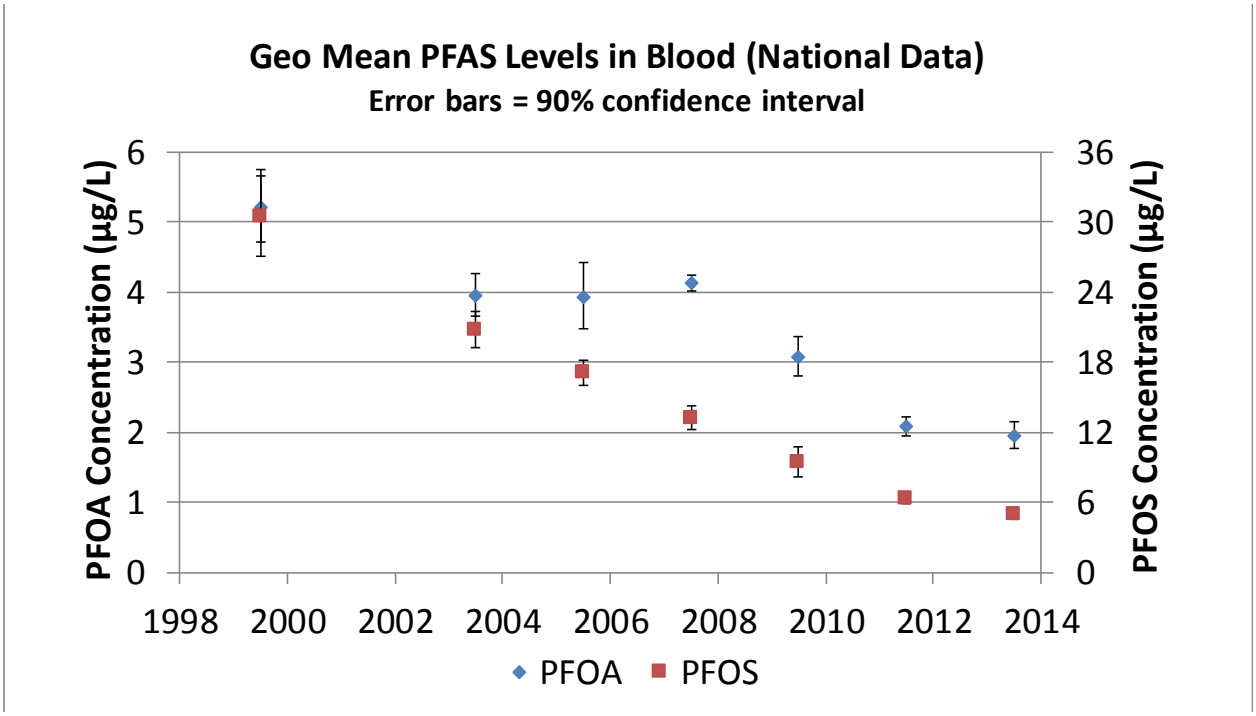

Figure 2 Geometric mean concentrations of serum PFOA and PFOS reported for the U.S. population, from Table 5-21 of the draft ATSDR Toxicity Profiles. Bars represent the 5th and 95th percentile concentrations, obtained from the more detailed NHANES data available online.

We thank ATSDR again for consideration of our comments.

Very truly yours,
SANBORN, HEAD & ASSOCIATES, INC.

Stephen G. Zemba, Ph.D., P.E.
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SGZ/RA: sgz
Attachment: Spreadsheet file calculations with serum PFAS arithmetic means

Acknowledgment

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