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Sarah Pillsbury
Administrator, Drinking Water and Groundwater Bureau
New Hampshire Department of Environmental Services
29 Hazen Drive, PO Box 95
Concord, NH 03302-0095

November 9, 2018
Via E-Mail

Re: Comments on Public Drinking Water and Groundwater Standards for PFAS

Dear Ms. Pillsbury:

We write on behalf of our colleagues at Sanborn Head to comment on the Maximum Contaminant Levels (MCLs) for four perfluoroalkyl substances (PFAS) under development by the New Hampshire Department of Environmental Services. Our comments follow on ensuing pages of this letter.

We greatly appreciate the opportunity to submit comments and hope to have similar opportunities for review and comment at future stages of the MCL development. We also are happy to discuss our comments, so please do not hesitate to contact us with questions.

Thank you again for this opportunity to participate in this process.

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

Stephen G. Zemba, Ph.D., P.E.
Project Director

Charles A. Crocetti, Ph.D., P.G.
Senior Vice President and Principal

Attachments:

Attachment A - Green Toxicology comments to ATSDR on its draft Toxicological Profile for Perfluoroalkyls
Attachment B - Sanborn Head comments to ATSDR on its draft Toxicological Profile for Perfluoroalkyls

Comments to the New Hampshire Department of Environmental Services on Developing Public Drinking Water and Groundwater Standards for PFAS

Sanborn Head respectfully submits these comments to the New Hampshire Department of Environmental Services (DES) for its consideration regarding the establishment of drinking water and groundwater standards for per- and polyfluoroalkyl substances (PFAS). We recognize and support DES's responsibility to protect public health and the environment, and we applaud the focus and attention DES has dedicated to this issue. We also recognize the concerns of the regulated community regarding the potentially high costs of meeting extremely low concentration standards for PFAS, especially if these standards prove to be more stringent than the levels necessary to protect public health. It is thus imperative, from our perspective, that DES set maximum contaminant levels (MCLs) for PFAS at levels that: (i) reflect scientifically sound estimates of adverse health effects based on a holistic analysis of available data, and (ii) balance the costs and benefits of establishing and enforcing the MCLs and resulting ambient groundwater quality standards (AGQS).

Selecting sound toxicological bases for PFAS standards is critical

DES must decide what observations from laboratory rodent studies constitute effects significant enough to merit serving as the basis of MCLs. Many of the reported observational effects in rodent bioassays that have served as the basis for current PFAS guidelines have been transient in nature, and in some cases dismissed as unlikely to be adverse effects by the authors of the studies. We recommend that DES base its proposed standards on a holistic review of the results of high-quality studies to ensure use of sound, peer-reviewed science. We also recommend that DES choose points of departure that represent significant health-related endpoints. We attach comments (Attachment A) submitted by Green Toxicology LLC on the Minimum Risk Levels (MRLs) recently proposed in the draft ATSDR Toxicological Profile for Perfluoroalkyls, since these comments contain recommendations on specific laboratory studies suitable for the development of reference doses.

DES should acknowledge the highly protective nature of the current U.S. EPA Lifetime Health Advisory

The U.S. Environmental Protection Agency's (EPA's) Lifetime Health Advisory (LHA) of 70 parts per trillion (ppt) for PFOA and PFOS in drinking water is highly protective of public health for the following reasons:

- The underlying reference dose (Rfd) is based on a reproductive and developmental study in which observed effects in mice (delayed ossification of phalanges and hastened puberty in male pups) were transient;

- Developmental health effects were not found to be statistically linked to PFOA in the C8 Panel Studies (the most comprehensive epidemiological studies conducted to date). Specifically, the studies found no associations with birth defects, miscarriages, stillbirths, and/or preterm/low birth weight;

- By default, EPA assumed that humans are potentially more sensitive to PFAS than laboratory animals, and they apply a factor of safety to account for this possibility. While this is standard "default" procedure, for PFAS it is not clear that humans are more

sensitive. Evidence indicates that rats and mice are more sensitive to PFAS-related effects than are humans, but the reference dose incorporates a safety factor for interspecies extrapolation that assumes the opposite (i.e., that humans are *more* susceptible than laboratory rodents);

- The assumed drinking water ingestion rate is 4.3 liters/day (L/d), a value more than twice as large as the 2 L/d ingestion rate typically included in MCLs and health advisories. The 4.3 liter/day ingestion rate is based on an upper percentile level of water ingestion by a nursing mother. If DES decides to adopt a similar assumption, it should evaluate whether the transfer of PFAS to the infant during nursing is similar in exposure characteristics to the pre-natal exposure that is implicit in the animal toxicity studies in which the PFAS dose is fed to the mother animals while pregnant.

- Non-drinking water exposures are assumed to account for 80% of the reference dose, even though the most recent measured PFAS concentrations in blood-serum indicate declining and much lower background exposure rates to PFOA, PFOS, and other PFAS. This assumption regarding background PFAS exposure allows only 20% of the reference dose to be allocated to the drinking water pathway as the Relative Source Contribution (RSC). DES acknowledged that the Relative Source Contribution from drinking water can vary from 20% to 80% per EPA guidance based on available evidence, with the default of 20% assumed in cases where evidence/information is lacking. However, in the case of PFAS, the blood serum data allow for estimation of the RSC, as detailed in our comments to ATSDR (Attachment B). If PFAS exposure from non-drinking water exposure pathways is assumed to be a more realistic 10% of the EPA reference dose of 20 ng/kg-d (providing an allowable RSC of 90%), then the health advisory value would increase to approximately 300 ppt based on 4.3 L/d of water ingestion, and approximately 600 ppt if the water ingestion rate is assumed at the default value of 2 L/d routinely used for other LHAs and federal MCLs.

- Use of higher reference doses potentially applicable to more serious health effects would also translate to higher levels of allowable exposure via drinking water. The question of what constitutes a serious health effect is subjective and debatable. However, if one defines a significant health effect as irreversible damage in animal studies (as opposed to transient effects), EPA could have justified selection of 150 ng/kg-d as the point of departure for its human equivalent reference dose (as opposed to the 20 ng/kg-d value that was selected).[1]

ATSDR's proposed draft Minimum Risk Levels (MRLs) should be critically examined

ATSDR has proposed MRLs for several PFAS at levels lower than EPA's 20 ng/kg-d reference dose and used the draft MRLs to issue Environmental Media Evaluation Guides (EMEGs) for drinking water.[2] Based on comments submitted to ATSDR by Green Toxicology LLC

[1] Of the candidate RfDs considered by EPA (as summarized in Table 5-2 of each of the drinking water health advisory documents for PFOA [EPA 822-R-16-005] and PFOS [EPA 822-R-16-004]), only the RfD of 150 ng/kg-d indicates a damage-based observation (liver necrosis). All other candidate RfDs reflect differences in body or organ weight, metabolic indicators, or transient developmental effects.

[2] ATSDR has issued EMEGs on the draft MRLs in advance of responding to public comments on the MRLs.

(Attachment A), Sanborn Head (Attachments B), and others, ATSDR's draft MRLs (and hence EMEGs) contain assumptions that are more extreme than necessary to protect public health. Some factors to consider include:

- The findings in the laboratory rodent studies used to derive proposed MRLs for PFOS and PFNA are minor, transient effects that may not be a reliable basis for robust toxicity values for purposes of human health protection. For PFOS, the effects used as the point of departure are delayed eye opening and decreased weight in newborn rat-pups. The study authors discount these observations as being insignificant, non-adverse effects. Without justification, ATSDR disagrees with the study authors.

- The proposed ATSDR MRL for PFOS incorporates a "modifying factor" of 10 to account for potential concerns over immunotoxic effects, which lowers the proposed MRL by the same factor of 10. This non-standard factor is improperly applied, since it is irrelevant to the key toxicity study and the effect relied upon as the point of departure for the MRL. An appropriate MRL based on concerns over possible risks of immunotoxicity should rely upon results from actual studies of immunotoxicity (if DES chooses this endpoint).

- For PFOA, ATSDR describes the effects used as the MRL's point of departure to be "less serious" health effects. As stated previously, we believe that reversible, transient effects observed in animal studies are an inappropriate basis for regulatory toxicity values.

- ATSDR incorporates modifying factors of 10 into its proposed MRLs for PFHxS and PFNA based on the availability of a limited number of studies, which lowers each of the proposed MRLs by a corresponding factor of 10. While it is true that fewer studies are available for these compounds than for PFOA and PFOS, many toxicologists suspect similar behavior and modes of action among these four compounds, and some states (CT, MA, and VT) have grouped these chemicals together. Since PFOA and PFOS have been extensively studied, the extra modifying factor is not needed for PFHxS and PFNA if suspected effects are similar. In this case, the additional modifying factor of 10 should be eliminated, since it is unnecessary, and certainly not evidence-based.

- All of ATSDR's proposed MRLs contain a standard default interspecies safety factor of 3 to account for the possibility that humans may be more sensitive to PFAS than laboratory rodents. Of course, standard default values are used to add protection in cases where evidence is lacking from toxicity studies. However, in the case of PFAS, ATSDR, EPA, and the scientific community at large recognize that 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, risk assessors should use PFAS-specific factors, and not default factors; in so doing, they would find that factors of less than 1 are most appropriate when extrapolating from effects in rats or mice to predictions for humans.

DES should critically examine assumptions used by other states in deriving PFAS standards

Vermont has adopted a 20 ppt drinking water standard using EPA's 20 ng/kg-d reference dose and the overly conservative assumption that 80% of PFAS exposure derives from non-

drinking water exposure pathways. Vermont assumes the same reference dose used by EPA in deriving its LHA, but it deviates from EPA by considering the dose received by a small infant/child (ingesting either water or formula prepared with drinking water), as opposed to the dose received by a nursing mother (the basis of EPA's LHA). EPA's approach is seemingly more consistent with the underlying animal study, in which the dose was received by mother mice while pregnant. The relevance of VT's deviation to the infant perspective is unclear, as the point of departure from the developmental toxicity studies involves exposure to the maternal animals during pregnancy. Metabolic and pharmacokinetic factors should be considered when making extrapolations from the results of the laboratory study, considering the differences in the modes of exposure.

New Jersey recently adopted an MCL of 13 ppt for PFNA based on concerns over increased liver weight in rodent studies. Increased liver weight is not necessarily an adverse health effect. In its 2014 Health Effects Support Document for PFOA, the EPA originally proposed increased liver weight as the basis of its 20 ng/kg-d reference dose. Upon limited but strident academic peer review, EPA abandoned increased liver weight as the point of departure for its reference dose.[3] Quoting an excerpt from Dr. Bruckner (one of the peer reviewers):

> "I do have a real problem with the scientific basis and soundness of certain conclusions in the document. The primary effect of PFOA in different species is increased absolute and/or relative liver weight. These are quite modest, reversible, non-specific effects that usually are not considered toxicologically significant."

DES should derive robust estimates of costs needed to meet PFAS MCLs and AGQSs

The costs associated with PFAS MCLs and AGQSs will include:

- Capital and operating costs of new treatment and infrastructure needed to treat public drinking water supplies such that MCLs are met.
- Site remediation will need to meet MCLs, and thus the potential costs associated with installation and operation of treatment systems for private drinking water wells, or the costs associated with supplying bottled water or hookups to public water supplies.
- Potential treatment costs imposed on wastewater dischargers, groundwater remediation systems, leachate disposal, biosolids, and other sources that may release PFAS to the environment and be subject to regulation.
- Costs associated with investigation, remediation, and monitoring of sites where PFAS concentrations exceed AGQS.

All of these costs will increase as potential MCL values are made more stringent, and so DES will need to consider costs as a function of potential MCL values. As an example of one of

[3] EPA Response to External Peer Review Comments on EPA Draft Documents: Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). May 2016. Accessed October 2018 at https://www.epa.gov/sites/production/files/2016-05/documents/response_to_pfoa_pfos_peer_review_comments_508.pdf

these components, the costs of drinking water treatment systems for private wells could be quite large and increase rapidly with more stringent MCLs. Our July 2017 review of the data from 1,782 samples of private drinking wells in PFAS contaminated areas of New Hampshire indicated that 12.8 percent (228 wells) had a detection of PFOA or PFOS above 70 ppt. If compared with the short-term health advisory issued by the EPA in 2014 of 400 ppt and 200 ppt for PFOS and PFOA, respectively, only 1 percent (18) of the domestic drinking water wells were above these levels. Current treatment for drinking water wells is focused on granular activated carbon, which can range up to $5,000 per typical domestic well to install (not including long-term operating costs).

In the New Hampshire example, the difference in treatment system costs alone between achieving 70 ppt and 400/200 ppt is estimated to be more than 10-fold. In this example, it would be $1.1 million to treat the wells above 70 ppt compared with $90,000 to treat the wells above 400/200 ppt. Considering this is only the cost of installing the treatment system at the drinking water wells, the cost of investigation, system maintenance and upkeep, and potentially remediating at a lower standard, is even more significant.

Note also that the areas/wells sampled thus far represent only a fraction of the total number of potentially impacted properties in NH. Also, as this example is only for PFOA and PFOS, additional consideration of PFHxS and PFNA would be expected to place even more wells over potential MCLs, and further increase costs.

DES should derive objective and scientifically-defensible estimates of health benefits (avoided costs) of achieving PFAS MCLs

Estimating the benefits of reducing PFAS levels in drinking water is a challenging task. Though heuristically simple in concept, determining dose-response functions and assigning monetary values to avoided diseases, developmental effects, and potential adverse health outcomes is difficult for PFAS. One calculation that can be done is the benefit associated with decreased cancer incidence, assuming (based on equivocal evidence) that PFAS exposure causes cancer. As a hypothetical example, assume that all PFAS exposure through drinking water could be eliminated, *i.e.*, the concentrations of PFAS in all drinking water sources could be reduced to zero. In that case, the economic benefit could be calculated as the cost associated with cancers caused by PFAS at levels currently present in drinking water. Using the following assumptions:

- A population-weighted average PFAS concentration of 20 ng/L in drinking water;[4]
- NH's 2017 population of 1.343×10^6 people;
- 2 L/d of drinking water consumed by each person of 70 kg average weight over an entire lifetime;

[4] A "ballpark" average concentration of PFOA+PFOS in NH public water supplies is estimated to be about 10 ng/l based on values presented by DES in a May 17, 2018 meeting, assuming 100 ng/l for values >70 ng/l, 5 ng/l for values <10 ng/l, and ignoring UCMR3 non-detects at elevated detection limits. Allowing for PFHxS and PFNA at a similar level provides an average estimate of 20 ng/l for the four PFAS.

- EPA's estimate of cancer potency slope factor for PFOA of 0.07 kg-d/mg (the value provided in EPA's 2016 *Health Effects Summary Document*, and assuming it applies to all PFAS);
- All PFAS-related cancers are fatal; and
- An economic value of $8,800,000 for a human life (a typical figure assumed by EPA in cost-benefit analyses pursuant to Clean Air Act regulations);

an estimated upper-end economic benefit value of $470,000 is calculated for the reduction from eliminating all PFAS from drinking water:

$$\text{Benefit} = \left(\frac{2\ \text{l/d} \times 20\ \text{ng/l}}{70\ \text{kg} \times 10^6 \text{ng/mg}}\right) \times \left(0.07\ \frac{\text{kg-d}}{\text{mg}}\right) \times (\$8.8 \times 10^6) \times (1.343 \times 10^6) = \$470{,}000$$

Consideration of less than complete reductions in PFAS concentrations (*i.e.,* MCLs >0), less than lifetime exposure periods, and the fraction of cancers likely to be non-fatal will all lead to smaller economic benefit.

It should be noted that the lifetime incremental cancer risk estimate, as set forth in the first portion of the above equation, is 4×10^{-8}, or 4 per 100 million, which is well below the *de minimus* 1 per million risk level used in the Superfund program to identify potentially significant risks. If all of the 1.3 million residents of New Hampshire each incurred this 4×10^{-8} excess lifetime risk, there would be about a 5% chance of developing a case of cancer within the population (based on the aforementioned assumptions).[5]

Estimation of the potential benefits of reducing non-cancer health effects needs to be explicit about the types of those health effects, the economic value of their prevention, and the number of individuals that might be involved based on exposure to PFAS at current levels of exposure and the reduced levels of exposure that would result from MRLs. Quantitative data to make these types of estimates will be difficult to ascertain, and will likely be quite uncertain. We encourage DES to accept additional input and comment on these estimates (if developed).

The above examples illustrate only some of the factors relevant to the cost/benefit analysis. We encourage DES to be both transparent and objective in this evaluation. It may also make sense to estimate the costs associated with environmental actions that might not go forward if DES continues to shift finite resources to PFAS mitigation. As examples, resource shifts that decrease efforts at reducing the levels of arsenic, lead, and other contaminants in drinking water, could present significant risks and public health costs.

[5] This simplified example does not take into account factors such as childhood exposure or potential variations over time (*e.g.*, possible decreases in concentrations of PFAS in drinking water in the future), but in an order of magnitude sense, does indicate a likelihood that PFAS exposure may cause no additional cancers in the New Hampshire population, based on current toxicity information.

Closing

Given the limited resources available to address environmental contamination and other significant human health or safety concerns (*e.g.*, repair of aging infrastructure for roads and drinking water distribution systems, WWTP plant upgrades, *etc.*), it is imperative that the PFAS MCL process results in a protective but reasonable standard that balances costs and benefits. If the MCLs are overly stringent, then the costs associated with implementation and compliance could well exceed the benefits associated with public health improvement. In particular, whatever marginal benefits would be gained by strictly regulating PFAS could be more than offset by deleterious impacts on other, perhaps more important public health problems in New Hampshire.

Attachment A

Green Toxicology comments to ATSDR on its draft Toxicological Profile for Perfluoroalkyls

Comments on ATSDR's *Toxicological Profile for Perfluoroalkyls*

Edmund A. C. Crouch, Ph.D. and Laura C. Green, Ph.D., D.A.B.T
August 20, 2018

Docket ATSDR-2015-0004

Introduction and Overview

The ATSDR *Toxicological Profile for Perfluoroalkyls* (Draft for Public Comment, June 2018) offers provisional minimal risk levels (MRLs) for four perfluoroalkyl substances (PFAS): perfluorooactanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS).

These MRLs are, in general, more restrictive than analogous reference values set by U.S. EPA or other agencies. For example:

- U.S. EPA's proposed reference dose for PFOA is 2×10^{-5} mg/kg/day;
- Health Canada's tolerable daily intake for PFOA is similar (at 2.5×10^{-5} mg/kg/day); and
- ATSDR's provisional MRL for PFOA is an order of magnitude more restrictive, at 3×10^{-6} mg/kg/day.

Unfortunately, ATSDR's provisional MRLs are no more justifiable than previously proposed guideline-values, and cannot be said to be reliable. Among other issues, the provisional MRLs for these four PFAS:

- Are not based on evidence of adverse effects in humans;
- Are sometimes based on questionable "principal studies";
- Do not reflect known or reasonably anticipated differences in sensitivities between and among laboratory rats, laboratory mice, and humans; and
- Fail to account for many recent, relevant studies.

With regard to the first point, it remains the case that epidemiologic and/or clinical evidence has so far failed to demonstrate that any PFAS harms human health. Notably, cancer patients in a phase 1 trial have been dosed with massive amounts of PFOA (up to 1.2 grams per patient per week), as an experimental chemotherapeutic drug, with no apparent harm to their livers

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(the organ most clearly and adversely affected by PFOA in laboratory rodents) or other organs (Convertino et al., 2018).[1]

Of course, high-level exposures to various PFAS, including PFOA, clearly *do* harm the health of laboratory animals, and it is entirely appropriate to base health-protective guidelines on exposure-response data derived from laboratory animal studies.

However, doing so requires considerable toxicological judgment — both in choosing which "principal studies" and dose-response data-sets to use, and deciding how to use them. The principal studies must be well-designed and executed, and the results should have been replicated. As explained below, for some of its four provisional MRLs, ATSDR's choice of principal studies is questionable; while for others, the data-sets are reliable enough, but ATSDR's use of them appears to be unjustified.

This is especially unfortunate because the text of the *Profile* itself is often quite informative and insightful. However, none of this insight is carried over into the derivation of the MRLs. Indeed, the latter — which are derived in Appendix A — are essentially uninformed by the almost 700 pages of text that precede them. This perplexing disconnect should not carry through to the final version of the *Profile* and its MRLs.

In this draft version, Appendix A assumes, by default, and without justification, a combined "uncertainty factor" of 300 (in three cases, a factor 10 of this is termed a "modifying factor") for each of its four provisional MRLs. So doing, Appendix A fails to conform with modern, human health risk assessment practice that, among other things, encourages the application (or at least consideration) of "chemical-specific adjustment factors" to provide more biologically-based, predictive, and still protective guidance values (see, for example, Meek et al., 1999, 2002 & 2011; Edler et al., 2002; WHO/IPCS, 2005; US EPA, 2014; Bhat et al., 2017).

For example, for each of its four provisional MRLs, the Agency simply applies a default factor of 10 to account for "human variability," but fails to justify this value. Of course, humans do vary

[1] As is typical for cancer chemotherapeutic drugs, these large doses did cause fatigue, nausea, vomiting, and diarrhea, which were considered tolerable by the patients. The draft *Profile* does not cite this paper, but should. The Convertino et al. (2018) paper was available five months prior to the release of the *Profile*; and ATSDR was aware of this clinical trial of PFOA, since the *Profile* cites a 2011 poster session abstract that describes it (MacPherson et al., 2011), and the poster *per se* is included in comments to U.S. EPA (Dupont, 2014). This information is especially important for the exposure assessment sections of the *Profile*, which at present indicate that it is manufacturing workers, and perhaps people drinking highly contaminated water, who are the groups receiving the largest doses of PFAS. For PFOA, at least, that is not the case. PFOS also has anti-tumor activity (Wimsatt et al., 2016), although we know of no clinical trials using PFOS.

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with regard to their sensitivities to the adverse effects of chemicals; but whether a factor of 10 is appropriate for accounting for populational variability *depends on the chemical and end-point at issue*.

For these four chemicals, interindividual differences in metabolic rate need not be accounted for, since these PFAS are not metabolized by either laboratory animals or humans.

Also, three of the four provisional MRLs are based on developmental effects associated with PFAS exposures of fetuses *in utero* and/or of neonates through lactational exposures. Of course these life stages are uniquely sensitive to the effects of developmental toxicants. There is no need to account for the possibility of some greater sensitivity of older children or of the elderly, for example, since for all other such subpopulations, development has already occurred.

In what senses, then, is a factor of 10 for "human variability" the "correct" value for these four PFAS MRLs? The Agency does not say, but it should. In several cases, the variability due to variation in elimination rates is known, and substantially less than a factor of 10; what would remain is only variability due to potentially differing sensitivities within the chosen, already most sensitive sub-population.

Also important, but also ignored in the derivation of the MRLs, are the *qualities* of the principal studies upon which the provisional MRLs are based.

For example, despite the availability of multiple high-quality studies on PFOA (most of which are cited in the *Profile* text), Appendix A relies for its MRL-derivation on results in rodents from a single poor-quality study[2] that fails to conform with internationally accepted study-guidelines, uses too few rodents, tests these rodents at only one dose-level, relies on unverified test-methods, has not been replicated (indeed, has been contradicted by more recent data), is strictly uncontrolled, uses the wrong basic measurement unit, and is otherwise entirely unsuitable. As detailed below, the "final" MRL for PFOA should be based on far more reliable data from guideline-based studies.

The *Profile* is based on literature searches that cover the period up until May 2016, so is now more than two years out-of-date. Had ATSDR searched for more recent literature (even for just papers that cited the principal studies that the Agency has selected), it would have found that the results of the principal study selected for the PFOA MRL, for example, *were not replicated* using standard test-methods.

[2] Two papers are cited as the principal studies (Onishchenko et al., 2001, and Koskela et al., 2016), but the laboratory mice reported on in the latter publication are simply a subset of the mice reported on in the earlier publication.

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In Appendix A, the Agency presents various approaches taken to estimate "human equivalent doses" (HEDs). Oddly, these approaches differ for the different PFAS, and they have been applied in a mutually exclusive fashion. As a result, and without justification, the Agency has ignored various high-quality studies, and relied instead on lower quality studies.

In particular, for PFOA and PFOS, the Agency relies on the use of the Wambaugh et al. (2013) modeled parameters to estimate the average serum concentration in experimental animals, thus ignoring any studies that did not use female CD-1 mice, female C57Bl6 mice, or male Sprague-Dawley rats (Table A-7). The Agency similarly ignores, for PFOS, any studies that did not use female CD-1 mice, female Sprague-Dawley rats, or Cynomolgus monkeys (Table A-15).

This unjustified approach was followed *even in cases where the serum concentrations were measured* in the cited studies, or in other studies using the same animals (but not analyzed in Wambaugh et al., 2013). However, with known dosing schedules, a good approximation to the volume of distribution, and even a single measurement at a known time point, the average serum concentration in experimental animals of PFOA and PFOS can be estimated; and in several of the studies reporting serum concentration measurements, additional information is provided that allows better estimates. The accuracy of this estimation is probably as good, for any single experiment, as the estimate obtained using the Wambaugh et al. (2013) modeled parameters. And, indeed, this approach using measured concentrations is taken for PFHxS and PFNA.

There is no reason to not use the same approach for PFOA and PFOS, relying, if necessary, on estimated parameters from other experiments on the mouse and rat strains not analyzed by Wambaugh et al. (2013). Indeed, if concentration measurements are available for the animals used in any study, then estimates using this approach should be compared with those obtained from the Wambaugh et al. (2013) modeling approach, and any discrepancies described and resolved. In particular, in Table A-7 for PFOA:

- Loveless et al., 2008 — serum PFOA concentrations were not measured in this experiment (which dosed for 29 total days), but a previous, cited experiment (Loveless et al., 2006) using the same animals at the same daily doses included measurements of serum concentration at 14 days. The previous measurements are quite sufficient to estimate average serum concentrations in Loveless et al., 2008.
- Abbot et al., 2007 — measured and reported serum PFOA concentrations.
- Cheng et al., 2013 — no suitable measurements in this report
- Albrecht et al., 2013 — measured and reported serum PFOA concentrations.

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And in Table A-15, for PFOS:

- Long et al, 2013 — no suitable measurements in this report
- Peden-Adams et al, 2008 — measured and reported serum PFOS concentrations.
- Guruge et al., 2009 — measured and reported plasma PFOS concentrations.
- Dong et al., 2009 — measured and reported serum PFOS concentrations.
- Dong et al., 2011 — measured and reported serum PFOS concentrations.
- Onishchenko et al, 2011 — no suitable measurements in this report.
- Wang et al., 2015c — measured and reported serum PFOS concentrations.
- Yahia et al, 2008 — no suitable measurements in this report.

Of course, the lack of measurements *within any particular report* should not end the quest for estimated serum concentrations; it is necessary to search related literature (particularly that published by, or cited by, the same authors) for experiments with serum concentration measurements in the same animals under similar experimental conditions. Why did the Agency fail to perform such a search?

In what follows, we present additional, hopefully constructive criticisms of the four provisional MRLs. We would note that assessing risks to human health for these compounds is not straightforward, and there is no one best approach. Nonetheless, we hope to explain how current evidence can be better used, and how future research may address uncertainties as to whether and how PFAS affect public health.

PFOA

The provisional, intermediate-duration MRL for PFOA is based on work in mice published by Onishchenko et al. (2011) and Koskela et al. (2016). The latter study relied on mice used in the former study, evaluated at a later age and for a different end point.

For at least the reasons detailed below, these "principal studies" fail to provide a sound basis for the derivation of an MRL. These investigations are nominally studies of developmental neurotoxicity (from prenatal exposures to PFOA or PFOS), but their methods are poor, and their results are unreliable. The Agency should choose different studies as the basis for its "final" MRL.

Groups of toxicologists, in regulatory agencies and elsewhere, have worked for decades to standardize the design of laboratory rodent studies (whether of potential drugs or other chemicals) for purposes of human health risk assessment. To investigate developmental

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neurotoxicity, the relevant guideline is *OECD Test Guideline (TG) 426* (OECD, 2007, based on U.S. EPA, 1998). As explained by Beronius et al. (2013):

> Both the US EPA and the OECD guidelines for [developmental neurotoxicity] DNT testing are structured to include investigations of developmental landmarks and behavioral ontogeny, motor activity, motor and sensory function, learning and memory, and neuropathology. For some of these categories several different validated test methods are available and the guidelines are largely flexible regarding which test method to include in the study design.

Unfortunately, the studies chosen by ATSDR for the PFOA provisional MRL fail to conform to the essential elements of the *Guideline*. For example:

- The *Guideline* calls for the use of rats as the study subjects, but Onishchenko et al. (2011) conducted their studies in mice.
- The *Guideline* calls for the use of at least three dose-groups, but Onishchenko et al. (2011) reported on only one dose-group.
- The *Guideline* calls for evaluation of 20 litters per dose-level, but Onishchenko et al. (2011) used only 6 pregnant dams in their exposed group (and 10 dams in their control group).
- The *Guideline* calls for the reporting of clinical observations of the test rodents, but Onishchenko et al. (2011) provide no such reporting.

Next, the Agency is not entirely accurate in its summarizing of the principal studies. For example, reviewing the results of Onishchenko et al. (2011), the Agency writes (page A-23), "Prenatal PFOA exposure was associated with increases in global activity and exploratory activity in adult offspring . . . ", but this is inaccurate. What was reported by the investigators was an increase in activity by male mice both during the first hour (habituation) and subsequently, but a *decrease* by female mice during the first hour of habituation, *with no change thereafter*.

Moreover, it is not known whether these observations, such as they are, in fact represent effects caused by to PFOA. This is because:

- The PFOA-exposed male mice were not matched with their controls. The 6 PFOA-exposed males were housed 3 and 3 in two cages, but the 8 control males were housed as 4 and 4 (these distributions are not explicitly stated, but are the only possibilities given the described experimental design). Activity levels in social groups might well depend on crowding levels.

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- The authors made no correction for their multiple comparisons. A quite large number of comparisons were made (at least 34 initial comparisons[3] can be seen in the reported results) with regard to behavioral-endpoints. Given this large number, the 5 "significant results" (at "$p<0.05$") that Onishchenko et al. (2011) report as being associated with PFOA might well have arisen due to chance alone, and not to any PFOA-induced effect. It is not possible to fully evaluate this problem, since the exact set of tests performed is not described.
- Some of the analysis was clearly performed post-hoc: the authors write, "… signs of altered locomotor activity in the exposed groups prompted us to extend the analysis of behavioral data …", which further compromises any statistics-based conclusions.
- There was no accounting for litter or individual animal effects in the analysis, and, as noted above, too few litters (6 for the experimental group, 10 for the control group; apparently there was no matching on litters) were used in any case to reach valid conclusions. The 5 "significant results" among males are clearly obtained from analyses of the wrong measure. All 5 of them could be due to excess activity by one mouse, for example, which would not correspond to a statistically significant effect. The analytical units here should clearly be mouse and litter, potentially taking into account interaction effects within each cage (since an over-active mouse might induce activity in other mice).
- In a more recent paper, several of the Onishchenko et al. authors (Spulber et al., 2014) state "… we re-analyzed the data we reported earlier [19], focusing on the novelty-induced hyperactivity in mice (Fig. 2 D), and found that mice exposed to 0.3 mg/kg/day PFOS display both less locomotor activity, and faster habituation (larger negative IOC value) as compared to controls and mice exposed to 3 mg/kg/day PFOS (Fig. 2 E)." Reference 19 is to the principal study, Onishchenko et al. (2011). Since Onishchenko et al. (2011) report only on exposure at 0.3 mg/kg/day PFOS, omitting the results subsequently documented at 3 mg/kg/day, this 2014 paper raises the possibility that higher dose(s) of PFOA might have also been tested, with the results similarly omitted from the 2011 report. Importantly, the higher dose (3 mg/kg/day) of PFOS resulted *in no effect* compared with control for at least one of the results reported as positive at 0.3 mg/kg/day, suggesting that the authors of Onishchenko et al. (2011) underestimated the variability in their experiments and/or applied incorrect statistical treatments.
- The apparatus used by Onishchenko et al. (2011) — cited as Trafficage, NewBehavior, Zurich, Switzerland; http://www.newbehavior.com/products/trafficage — is unusual, indeed almost unique (used apparently by only one group), for such studies, and it has not been calibrated against standard measures. A subsequent version of the apparatus (cited as TraffiCage, TSE-Systems, Germany; https://www.tse-systems.com/product-details/trafficage) has distinct differences (6 coils in place of 5) and requires special

[3] Counting males and females together, at least the following: 2 for the locomotor tests, 6 for the novelty comparisons in Figure 2, 10 in Table 2, 12 in Table 3, 2 in Figure 4, 2 in Figure 5.

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computer code to "correct" the measurements (*e.g.* Dudek et al., 2015). No such "corrections" were applied in the cited experiment, or at least none were mentioned.

- There is no reference to a tested protocol that would eliminate potential biases (*e.g.* even if the control and test animals were housed in the same room, they might be differentially sensitive to external influences such as vibrations, even if housed on the same bench, due to resonance locations in the building or support structures) and potential corrections needed (*e.g.* the shielding effect of tissue on the transponders might affect the recorded location of the animal vary with the orientation of the animal within the cage). The need for extensive protocol testing is apparent in the results of tests carried out on similar apparatus for rats (Redfern et al., 2017).
- The manufacturers of both the originally cited and the subsequent version of the TraffiCage apparatus failed to respond to emails from us requesting technical details of their apparatuses, and no such details are provided on their web sites (the first now re-directs to TSE-Systems), so it is not possible to even theoretically evaluate the minimal experimental details provided. The "References" on the TSE-Systems site is simply a Google Scholar search. Certain technical details (the time resolution) of the apparatus used by Onishchenko et al. (2011) are given different values[4] in subsequent publications (Spulber et al. 2014, 2015).

Further doubt on the validity of any causal connection between exposure to PFOA and the effects claimed in Onishchenko et al. (2011) is raised by (i) the complete lack of agreement between effects claimed in male and female mice in the results obtained, and (ii) the subsequent failure to replicate the results (Goulding et al., 2017).

Moreover, the experiments of Abbott et al. (2007) on PPARα-null mice, and of Albrecht et al. (2013) on PPARα-null and PPARα-humanized mice, showed that developmental toxicity in the mouse is dependent on the expression of mouse PPARα and not human PPARα. Thus, even were the effects reported by Onishchenko et al. (2011) in the mouse actually caused by PFOA, *human fetuses and neonates would be expected to be relatively resistant* to such effects.

The second paper (Koskela et al., 2016) selected as the basis for the provisional MRL examined an outcome in the female mice used in Onishchenko et al. (2011) when they had grown to 13 or 17 months old. This experiment was again uncontrolled, in that the dosed and control groups were of different weights, and the outcome measures were such that, as stated by the authors, "[t]he mild effects seen here are probably explained to some degree by increased body weight and thus increased load on the long bones …" although of course without the necessary

[4] 50 ms and 20 ms respectively. However, while the time-stamp provided by the apparatus might provide such resolution, the actual measurements using the RFID transponder types described take somewhat longer, and a full measurement cycle over the 5 coils would take longer still (typically about 60 ms and 500 ms respectively, based on Redfern et al., 2017).

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controls it is impossible to rule out (or rule in) some effect of PFOA exposure. Once again, the observations of Abbott et al. (2007) and Albrecht et al. (2013) on the PPARα-dependence of developmental effects in mice is relevant (Table 2-3 classifies the outcome claimed by Koskela et al., 2016, as developmental).

In neither experiment were the reported outcomes determined, *by ATSDR itself*, to be serious effects. Table 2-3 of the *Profile* classifies the claimed "Increased locomotor activity in adult offspring" listed for Onishchenko et al. (2011) as a "Less serious" effect. Table 2-3 fails to note that this effect was only seen in male offspring, and the opposite effect was transiently seen in female offspring, and only during novelty induced activity. The bone differences seen by Koskela et al. (2016) were also classified in Table 2-3 as "Less serious" effects. Why does Appendix A fail to mention these caveats? Surely MRLs should be based on effects deemed to be seriously adverse: if not, why bother making this distinction throughout the text?

PFOS

The Agency chooses to base its provisional MRL for PFOS on "[D]elayed eye opening and decreased pup body weight," as reported in a two-generation rat study by Luebker and colleagues, 2005 (page A-36). This is a questionable choice, given what the study authors themselves write about these two "effects". In particular, Luebker et al. (2005) note (*emphases added*):

> 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*. . . .
>
> *Only transient* reductions in body weights occurred during mid-lactation in the F_2 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.

Nowhere in its discussion of this "principal study" (pages A-41-A-42) does ATSDR mention these important caveats. Why? If ATSDR maintains this study as the basis for the PFOS MRL, then it should provide experimental evidence (a) that a 0.6 day delay in eye opening is not within normal variability for this strain of rats, and (b) that the larger litter size cannot explain the reductions in body weight.

Not only does ATSDR fail to explain why it disagrees with the study authors concerning the lack of toxicological significance of the relied-upon PFOS-associated effects: the Agency also fails to explain what it believes these effects mean for the development of human infants. Indeed, while eye opening is one developmental milestone in rodents, there is of course no direct

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analogue for humans. Further, there are many other developmental milestones, and/or indications of developmental toxicity, typically measured in two-generation rodent studies; and these are not, apparently, affected by PFOS at the effect-level chosen by ATSDR from Luebker et al (2005). Such typical rodent developmental effects include: olfactory discrimination, swimming performance, nocioception (measured by the tail flick test), sensorimotor gating-prepulse inhibition, exploratory behavior, and social (play) behavior (see, for example, Schneider & Przewlocki, 2005). Is it significant that PFOS, at the point of departure, is not known to affect any of these developmental and/or neurobehavioral endpoints? ATSDR does not say.

Separately, and also perplexingly, ATSDR derives its MRL (based, nominally, on Luebker et al., 2005) by applying a "modifying factor" of 10 to account (page A-42) "for concern that immunotoxicity may be a more sensitive endpoint of PFOS toxicity than developmental toxicity. This seems poorly justified, at best. The Luebker et al. (2005) is not a study of immunotoxicity, and no "modification" of dose-response data from it can be used to predict immunotoxicity even in rats, let alone in humans.

If the Agency believes that PFOS is immunotoxic at or near environmentally-relevant exposures, then it should rely directly on other studies that actually address immunotoxicity. But if the Agency believes instead that such studies are no more than suggestive, then it should discount them.

At the least, the effect-levels in such immunotoxicity studies should be compared with those in the principal, currently selected study: if the effect-levels in the immunotoxicity studies are comparable or larger than those in the principal study, then clearly no further "modifying factor" is necessary; while if the effect-levels are smaller, then any "modifying factor" need not exceed the ratio of the effect-levels (and in this case the immunotoxicity study would effectively become the principal study).

If ATSDR is concerned that PFOS might be immunotoxic at environmentally-relevant exposures, then it should propose specific additional research aimed to uncover such an adverse effect, which, if found, could provide a reliable, relevant data-set for purposes of human health risk assessment.

As it stands, though, the Agency bases its provisional MRL for PFOS on "critical effects" (page A-36) in neonatal rats that the study-investigators themselves deem to be "slight", "transient", and not "toxicologically significant;" and then compounds its questionable choice by dividing by an arbitrary factor of 10 that appears to be more "precautionary" than it is scientific.

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PFNA

The Agency bases its provisional MRL for PFNA on "[D]ecreased body weight and developmental delays" as reported in a two-generation mouse study by Das et al., (2015; page A-57). This study utilized four dose-rates (1, 3, 5, and 10 mg PFNA/kg-day), and 8 to 10 dams per dose-group. The authors report, "Mouse pups were born alive and postnatal survival in the 1 and 3 mg/kg PFNA groups was not different from that in controls." Offspring that had been exposed at 3 mg/kg (but not at 1 mg/kg) gained weight at reduced rates (starting at postnatal day 7); and both eye-opening and vaginal opening separation were delayed in offspring at 3 mg/kg (but not at 1 mg/kg).

With regard to mechanism of action, Das et al. (2015) note the "robust activation of peroxisome proliferator-activated receptor-alpha (PPARα) target genes by PFNA that resembled the responses of PFOA." And as expected and reported by Wolf et al. (2010), PFNA failed to induce these adverse effects in mice that had been genetically engineered to lack this important receptor.

Accordingly, as noted above, human fetuses and neonates would be expected to be *considerably less*, not more, sensitive to these PFNA-induced, PPARα-mediated effects.[5] But again, the Agency derives its MRL by assuming that human offspring could be up to 30 times more sensitive than the "average" mouse. The Agency again fails to even discuss the genuine uncertainties in its 30-fold "uncertainty factor," let alone to justify its choice of this precise and,

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[5] PPARs are present throughout the plant and animal kingdoms: many forms of these receptors have so far been identified (see, for example, Tyagi, 2011, for an authoritative review). The specific molecular forms and structures of these receptors differ among rats, mice, monkeys, and humans; and some of these differences profoundly affect how PFAS and other PPAR-agonists affect rodents, for example, as opposed to humans. Tyagi, 2011 note (emphases added):

> PPARs were identified in rodents in 1990 and these belong to a nuclear hormone receptor superfamily containing 48 members. *But, these agents are associated with no proliferation in the human beings*. Structurally, PPARs are similar to steroid or thyroid hormone receptor and are *stimulated in response to small lipophilic ligands*. *In rodents*, a large class of structurally related chemicals including herbicides, industrial solvents, and hypolipidemic drugs lead to significant increase in the number and size of peroxisomes in the liver and may cause liver hypertrophy, liver hyperplasia, hepatocarcinogenesis, and transcription of genes encoding proximal enzymes. PPARs mainly exist in three subtypes; α, β/δ, and γ, each of which mediates the physiological actions of a large variety of FAs and FA-derived molecules. Activated PPARs are also capable of transcriptional repression through DNA-independent protein-protein interactions with other transcription factors such as NFκB signal activators and transducers of transcription STAT-1 and AP-1 signaling.

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based on the evidence, overly large value. This failure should not carry through to the final version of the *Profile*.

Some 10 epidemiological studies have addressed the hypothesis that PFNA affects birth outcomes: results from these studies have generally failed to support this hypothesis.

In particular, PFNA exposure-levels have been found to not correlate with birth weights (Monroy et al., 2008; Chen et al., 2012; Arbuckle et al., 2013; Robledo et al., 2015; Bach et al., 2016; Lee et al., 2016; Lenters et al., 2016; Shi et al. 2017) or with other developmental indices, such as birth length or ponderal index (Bach et al., 2016; Shi et al., 2017). Wang et al. (2016) reported that PFNA and four other PFAS all correlated inversely with the birth weight of girls, but not of boys.

The text of the *Profile* (page 377) does note:

> No consistent associations for alterations in birth weight were found for . . . PFNA . . . Overall, no associations were found between serum PFOA, PFOS, PFHxS, PFNA, or PFUA and increases in the risk of low birth weight or small for gestational age infants. No consistent results for risks of birth defects have been found . . .The available epidemiology data do not suggest associations between perfluoroalkyls and IQ or scholastic achievement for PFOA, PFOS, PFHxS, PFNA, PFDeA, PFUA, or PFDoA. Similarly, no associations were found between PFOA, PFOS, PFHxS, PFNA, or PFDeA and increased risk of ADHD; several studies have found decreased risk of ADHD.

Yet Appendix A, in deriving an MRL for PFNA based on the developmental endpoints in mice noted above, fails to note a lack of support from the rather abundant epidemiologic database. This seems an important omission, and should be rectified in the final version of the *Profile*.

PFHxS

The Agency bases its provisional MRL for PFHxS on "[T]hyroid follicular cell damage" supposedly reported in rats, citing Butenhoff et al. (2009) and Hoberman and York (2003). The 2003 report is unpublished, and although cited several times in the text of the *Profile*, not discussed. It apparently forms the basis of the published, 2009 paper. The agency should provide a reference to this unpublished paper that allows an interested person to locate it: a suitable form would be something such as, "Available in EPA Administrative Record AR-226, copies of which may be requested on CD-ROM from the EPA Docket Office by calling 202-566-0280 or sending an email request to: oppt.ncic@epa.gov."

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For at least two reasons, ATSDR's choice is questionable.

First, there is no evidence that the rats' thyroid follicular cells were "damaged" by PFHxS. Instead, as Butenhoff et al. (2009) note, high doses of PFHxS did, as expected, affect exposed rats' livers – effects that the Agency itself clearly rejects as irrelevant for purposes of human health risk assessment (see page A-49). The effects seen in the thyroid glands of the male (and not female) rats were (i) only indirect, being secondary to induction of the rats' livers' microsomal enzymes and, in any event, (ii) not "damage". The Butenhoff et al. (2009) study makes this point clear: but Appendix A obscures it.

Second, follow up studies in mice (Chang et al., 2018, not cited by ATSDR) found no such effects in the thyroid of either male or female rodents, neither in adults nor in the offspring. The Chang et al. (2018) study examined reproductive and developmental toxicity in CD-1 mice, with additional mice added for toxicokinetic studies. The authors report (emphasis added):

> In the current study of PFHxS, there was no effect on TSH in the adult F_0 mice or in the F_1 pups when serum TSH was measured at multiple times during their development; and, most importantly, there were no effect on thyroid histopathology. Therefore, there is *no evidence to suggest that perfluoroalkyl sulfonates such as PFHxS and PFOS impact thyroid homeostasis*.

This paper is not cited in the *Profile*, but should be.

In estimating an HED from the study of Butenhoff et al. (2009), the Agency used the half-life derived by Olsen et al. (2007) in 26 retired occupationally exposed workers, only two of whom were women (both likely past menopause). The Profile should note that Li et al. (2017a,b) have derived half-lives for PFOS, PFHxS, and PFOA in 106 members of the general population, with separate estimates for men and women ages 15–50. For PFHxS (and for PFOS), the half-life for younger women was significantly less than for men, with menstrual blood loss potentially accounting for some of that difference. If the final MRL were to be based on reproductive effects, then the extrapolation to humans should be based on this smaller half-life, since women of child-bearing age would be the susceptible population. Of course, HEDs for other end-points in the rodents should be compared, and use of a longer half-life might be appropriate for estimating HEDs for such other end-points.

We note that Ramhøj et al. (2018) examined the effect of PFHxS and a mixture of PFHxS and twelve endocrine disrupting chemicals on reproductive toxicity in Wistar rats, but the F_0 generation was limited to the dams. Evaluation of these studies should be added to the *Profile*.

Overall, though, there are so far rather few published toxicologic studies on PFHxS. Perhaps deriving *any* MRL for this specific PFAS is premature? Alternatively, perhaps additional,

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unpublished studies could be located (and made publicly available): if relevant and reliable, could they be used to derive a more reliable MRL?

Additional observations

This set of compounds is typically referred to as "perfluorinated alkyl substances," and so abbreviated as PFAS. The Agency chooses instead to refer to them as "perfluorinated alkyls," which is both nonstandard and ungrammatical, the correct term in chemistry being, for example, "alkyl group". Why did ATSDR make this odd choice? We recommend against it.

We noted two typos in Appendix A in connection with PFHxS. At page A-9, the paragraph beginning "PFHxS," at line 3, the estimated half-life given by Olsen et al. (2007) was 3,109 days, not 3,102; and at line 5, the highest final concentration was 791 ng/mL, not 1,740 ng/mL (which was the highest final concentration of PFOS, not PFHxS).

Concluding remarks

Through no fault of the Agency's, ATSDR's *Toxicological Profiles*, and especially its MRLs, often stir controversy. The current *Profile* and set of MRLs are no exception. Even mainstream science news reports contained headlines and stories such as (*E&E News*, Jun. 20, 2018):

> ***After controversy, U.S. releases report showing elevated health risks from nonstick chemicals***
>
> President Donald Trump's administration has released a politically charged toxicology report about nonstick chemicals showing they can endanger human health at significantly lower levels than the Environmental Protection Agency (EPA) has previously called safe. . . .

Of course, the statements are inaccurate, in several respects, but perhaps that is to be expected. Press releases from various activists' groups were more alarmist still.

Because of their importance, the Agency's MRLs, even just the "provisional" MRLs, must be strongly evidence-based. Moreover, the ATSDR must take special care to succinctly and transparently convey the many uncertainties that surround its MRLs: U.S. EPA does this with regard to its reference dose-values; but ATSDR's standard explanations of its MRLs fall short.

For example, ATSDR must make plain, to the public, which of its MRLs are based directly on evidence from human studies, and which (all four in this case) are instead extrapolated solely from evidence in laboratory rats and/or mice. Perhaps a simple designation could be devised to mark the MRLs: such as, "Acute MRL; based on human studies"; or "Chronic MRL; based on studies in rats."

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As detailed herein, the Agency's provisional MRLs for all four PFAS should be revised. In some cases, as noted above, the Agency chose unreliable studies as their sole basis for an MRL. The Agency should choose differently going forward. In other cases, the chosen studies are reliable, but the Agency's uses of them are questionable.

We expect that ATSDR has many constraints, resource-wise and otherwise, and recognize that objective analysts may differ among themselves as to the "correct" way to assess risks to human health from given chemical contaminants. Nonetheless, there is now considerable scientific knowledge regarding at least PFOA and PFOS, if not the other two PFAS. ATSDR can and should do better as it works to finalize its MRLs.

Acknowledgement
We received no funding for these comments, and have no conflict of interest. We are solely responsible for any errors.

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Attachment B

Sanborn Head comments to ATSDR on its draft Toxicological Profile for Perfluoroalkyls

SANBORN HEAD

Building Trust. Engineering Success.

August 20, 2018

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Division of Toxicology and Human Health Sciences
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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.

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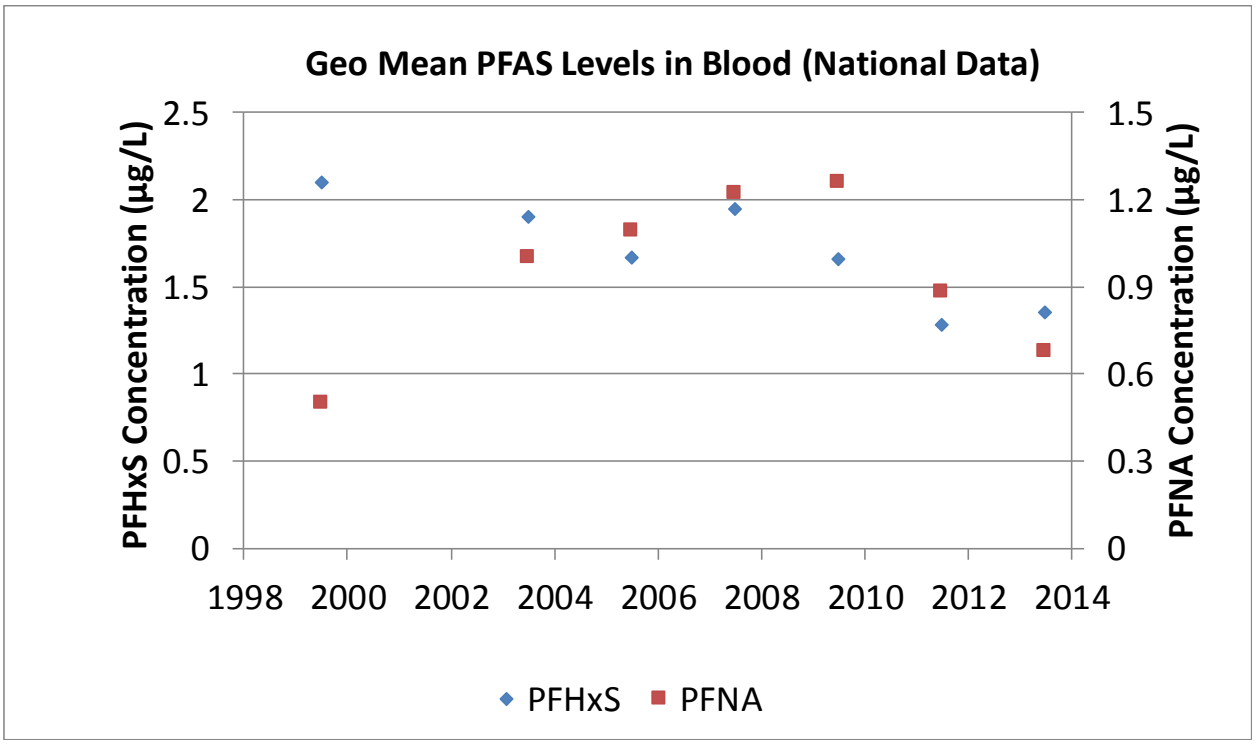

Figure 1 Geometric mean concentrations of serum PFHxS and PFNA reported for the U.S. population, from Table 5-22 of the draft ATSDR Toxicity Profiles

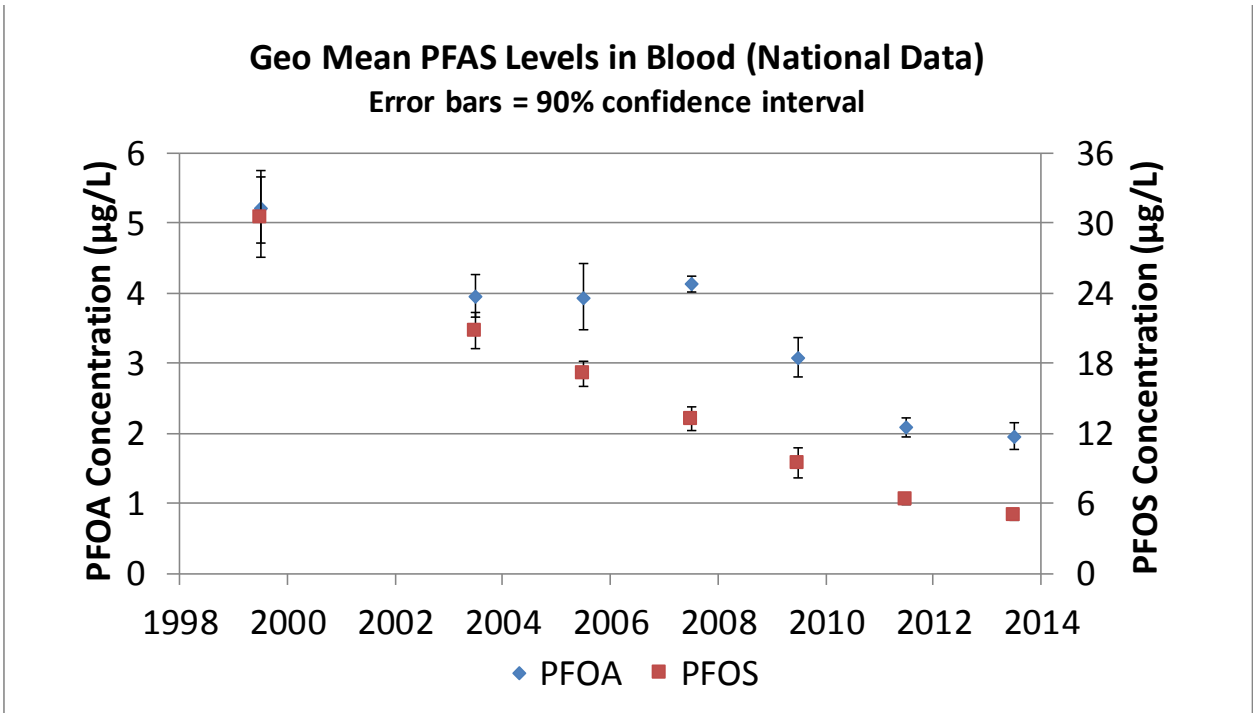

Figure 2 Geometric mean concentrations of serum PFOA and PFOS reported for the U.S. population, from Table 5-21 of the draft ATSDR Toxicity Profiles. Bars represent the 5th and 95th percentile concentrations, obtained from the more detailed NHANES data available online.

We thank ATSDR again for consideration of our comments.

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

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SGZ/RA: sgz
Attachment: Spreadsheet file calculations with serum PFAS arithmetic means

Acknowledgment

Sanborn Head sponsored the development of these comments, with additional, partial support from clients involved in the management of solid waste, biosolids, and other organic residuals.