

Dr. Chui and the SAB members,

December 23, 2021

Thank you again for the opportunity to provide comments regarding the documents the SAB has been asked to review regarding the derivation of draft maximum contaminant goals for PFOA and PFOS. I hope that my comments provided here and organized by document and charge question are useful to the SAB and the EPA.

Kind regards,
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Derivation of Draft Maximum Contaminant Level Goals for PFOA and PFOS

Study Identification and Inclusion

1. EPA used systematic review methods consistent with the current ORD systematic review practice to ensure transparency and completeness of literature identification, sorting, and study quality evaluation. Is the process clearly described? Please identify additional peer reviewed studies that the panel is aware of that could inform toxicity value derivation.

During the December 16, 2021, public meeting it was clarified that systematic review methodology was only used to conduct the literature search and screening steps of the document preparation. That systematic review methodology was NOT used for the evidence synthesis and evidence integration points was not clearly communicated in the PFOA and PFOS draft documents, which used headers such as “2.0 Methods for PFOA/PFOS Health Effects Systematic Review.” It was also stated during the December 16 public meeting that up to 30 scientists worked collaboratively to draft the evidence synthesis and evidence integration sections. This explains the apparent lack of consistency across the documents in how bodies of evidence were summarized and how conclusions were drawn. It is not clear why The Office of Water chose not to use existing evidence synthesis and integration tools while preparing these draft documents, as doing so would seem ever more important given the high number of individuals working on this document. At the very minimum, the Office of Water should be more clear and transparent that systematic review methodology was not used throughout the entirety of the process. To improve the reliability and strength of the assessments, however, I recommend the evidence synthesis and evidence integration steps to be significantly restructured to better align with the available guidance in the ORD Staff Handbook for Developing IRIS Assessments (US EPA 2020).

It is important to note the numerous deficiencies and inconsistencies from systematic review methodology noted throughout the documents. Of utmost importance, EPA did not prepare and publish a protocol detailing the conduct of these reviews *a priori*. This critical step of systematic review ensures that the final product is transparent and unbiased, and completing this step would have not streamlined and strengthened the work of the Office of Water. The ORD Staff Handbook states:

“The protocol is a central component of a systematic review. It is intended to improve transparency and reduce bias in the conduct of the review by describing the review question and methods in advance (CRD, 2013; Higgins and Green, 2011a; IOM, 2011). The IRIS systematic review process involves the development and use of a protocol that presents the detailed methods for assessment development” (US EPA 2020).

The lack of an *a priori* published protocol is especially concerning given that the plan for these assessments was to, in some way, build off of the existing literature summaries that informed the 2016 Lifetime Health Advisories (LHAs) for PFOA and PFOS. Specifically, the methods section lacks clarity as to how the existing information from the 2106 LHAs would or would not be used in deriving overall hazard identification conclusions. This lack of clarity is also found throughout

the results section, with some sections providing summaries of the data that were in the 2016 LHAs and other sections lacking such summaries. Further, it does not make logical sense to only draw conclusions from data published since the 2016 LHAs, even when earlier data on the same health outcome has already been published. Why would the entirety of the literature for a health effect not be considered? This is especially concerning given that the 2016 LHAs were not conducted using systematic review methodology, and therefore it is possible that relevant studies may not have been incorporated. The importance of this oversight is magnified when one considers that EPA has acknowledged the need to derive outcome specific reference doses in order to facilitate estimation of risks from mixtures of PFAS that act on the same health outcome. Finally, this is not consistent with other work coming from ORD, specifically the EPA's Integrated Risk Information System (IRIS), as there was an *a priori* published protocol for the conduct of reviews on PFBA, PFHxA, PFHxS, PFNA, and PFDA (US EPA 2021a). It is unclear why the reviews of PFOA and PFOS were not handled in the same manner.

EPA states that it used methods consistent with the current ORD systematic review handbook, but does not indicate if it had made any changes to the process in response to feedback from the National Academies of Science (NAS) review that has occurred (National Academies of Sciences and Medicine 2021). Here I also echo concerns and feedback raised by the NAS committee (National Academies of Sciences and Medicine 2021). First, EPA has been very loose with terminology throughout the documents, making it very difficult to understand what EPA evaluates at each step. For example, what is the difference between “study quality”, “study validity”, and “study risk of bias”? These all seem to be evaluated simultaneously, but a description of what each measurement is and how it may or may not differ from other measurements is not provided. Importantly, the EPA also asks the SAB if it agrees with the strong vs. suggestive evidence designations, yet these designations are never defined in the documents. NAS has also recommended that EPA acknowledge the importance of funding source and potential financial conflict of interest during the risk of bias analysis, but EPA has not done so in this evaluation (National Academies of Sciences and Medicine 2021). Not acknowledging the potential for conflict of interest based on study funding is especially alarming given that EPA recently elected to have industry submitted data for the PFAS chemical GenX reexamined by outside experts at the National Toxicology Program. The reanalysis came to a different conclusion regarding the severity of the effect, which ultimately influenced the final evaluation of GenX by EPA.

The evidence synthesis and evidence integration sections are likewise confusing and poorly described. Details for how these steps are conducted are not provided in the methods, and the results are not presented in a similar format as other recent EPA documents, for example the toxicological review of PFBA (US EPA 2021b). The reasoning that was provided in the December 16, 2021, meeting was that there were many scientists working on these sections. This, however, only serves as a clear rationale for why systematic evidence synthesis and evidence integration methodologies are needed.

An additional point of concern is how EPA handled and utilized mechanistic data in the PFOA and PFOS review. Here and in other documents, EPA specifically calls out the utility of new approach methods (NAMs) for informing hazard identification and risk assessment approaches. Specifically the accompanying document “EXTERNAL PEER REVIEW DRAFT Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)” states that the component-based mixture frameworks, “allow for the integration of information derived from other health assessment data sources (e.g., other federal, state, international), available human epidemiological and experimental animal hazard and dose-response data, and information from New Approach Methodologies (NAMS)” and further

“considering the lengthy and resource-intensive processes and study protocol (e.g., OECD Test Guidelines-type studies) typically involved in generating traditional repeat-dose bioassay data for human health assessment of chemicals, leveraging NAMs could potentially serve an important role for PFAS screening and assessment, including in a mixture context” (US EPA 2021c). However, in the “External Peer Reviewed Drafts for PFOA and PFOS presented to the board, *in vitro* and mechanistic data is not included, rather it is marked as “supplemental material,” thereby limiting its utility for the future read across efforts described by EPA elsewhere (US EPA 2020, 2021d).

The importance of EPA’s decision to ignore mechanistic data is especially apparent in the sections investigating the carcinogenicity of PFOS and PFOA. On page 289 of the PFOS document, EPA states “Additional analysis on the mechanistic actions of PFOS on cancer health outcomes is pending and is expected to be completed after the EPA SAB review” (US EPA 2021e). A similar statement is also found in the PFOA document (US EPA 2021d). It is unclear why EPA would put before the SAB an incomplete analysis of the carcinogenicity of PFOA and PFOS, especially in light of the recent draft determination from California’s Office of Environmental Health Hazard Assessment (OEHHA) (OEHHA 2021a). OEHHA documents sufficient evidence for seven key characteristics of carcinogens for PFOS: is genotoxic, induces epigenetic alterations, induces oxidative stress, induces chronic inflammation, is immunosuppressive, modulates receptor-mediated effects, and alters cell proliferation, cell death, or nutrient supply; and some evidence for an additional key characteristic - causes immortalization (OEHHA 2001, 2021a; Smith et al. 2016). OEHHA’s findings are greatly supported and enhanced by the inclusion of mechanistic data. EPA states in the methods that *in vitro* and mechanistic data will be used, but fails to do so in this case, pushing the analysis off to a later, future assessment.

Noncancer Hazard Identification

1. Please comment on the health effect/outcome categories identified from the review of the available literature. Do you agree with the strong vs. suggestive evidence designations for the various health outcome categories? Do any other health systems or endpoints need to be considered for POD derivation?

The draft documents for the analysis of PFOA and PFOS do not define “strong evidence” or “suggestive evidence” (US EPA 2021d, e). Further, these categories for evidence integration are not the same as those described in the ORD Staff Handbook (Tables 11-3, 11-4, and 11-5) (US EPA 2020). Therefore, it is unclear how the SAB can agree or disagree with these designations. This again highlights the importance of having an a priori protocol available and a commitment to following all steps of a systematic review methodology.

Here and in other documents EPA has highlighted the importance of deriving organ specific reference doses (RfDs) that could inform future mixtures or cumulative risk analyses (US EPA 2021b, c). The EPA’s IRIS program has followed a transparent systematic review methodology to derive draft RfDs for other PFAS. The Office of Water should commit to the same for PFOA and PFOS, given that PFOA and PFOS are likely to serve as index chemicals by which all other PFAS may be judged. Therefore it is imperative that RfDs be derived for all health outcomes associated with PFOA or PFOS for which there is sufficient evidence. In other words, it is important to have as many PODs calculated as there are health effects associated with

exposure because of the potential for mixture calculations and determinations of health costs associated with exposure (US EPA 2021c, f).

2. Elevation of liver serum biomarkers in humans is frequently used an indication of liver injury, although it has not been shown to be as specific as functional tests, such as histology findings and liver disease (Boone, 2005, HERO ID: 782862). However, greater than 2-fold increases in alanine aminotransferase (ALT) activity, the most sensitive test of hepatocellular injury in humans, above the upper limit of normal are considered indicative of hepatocellular injury. EPA concluded that the available data in adults show a consistent positive association between PFOA and/or PFOS exposure and increased serum ALT levels in the epidemiological literature. However, this response was not selected for dose response modeling because 1) the magnitude of the effect was not large compared to control levels; and 2) concerns about the clinical relevance of the findings and non-specificity of the biomarkers relationship to adverse liver injury and disease.

Here again, the lack of consistency across the document and across EPA offices is noted. In Section 3.3.1.2 Study Quality of Human Hepatic Evidence, it appears that study quality was only evaluated for the 22 new epidemiology studies obtained since the completion of the 2016 HESD. This is in contrast to Section 3.3.2 Animal Evidence for Hepatic Effects which states, “There are 12 studies from the most recent literature search conducted in 2020 and 7 key studies from the 2016 PFOA HESD [U.S. EPA, 2016, 3603279] that investigated the association between PFOA and hepatic effects. Study quality evaluations for these 19 studies are shown in Figure 55” (US EPA 2021d).

The decision to derive a POD based on the hepatic effects described in the charge question should not be based only on the evidence which was published after the release of the 2016 HESD, and yet that is what EPA seems to have concluded in Section 3.3.3.4. Evidence integration using a systematic review framework would have considered both the strength of the evidence in the entire body of human epidemiological research and the strength of the evidence in the entire body of animal toxicological research. EPA did not present these two complete bodies of evidence in a way that supports the conclusion to not derive a POD.

Cancer

1. Cancer classification for PFOA/PFOS

- A. PFOA: Based on new cancer studies identified since the 2016 PFOA Health Advisory (HA), EPA concludes that the available cancer data for PFOA indicate a ‘likely carcinogen’ categorization which is a change from ‘suggestive’ in the 2016 HA. Does the panel agree with the ‘likely’ designation based on the new evidence? If yes, is the rationale clearly described? If no, please provide an explanation for arriving at a different conclusion.

- B. PFOS: Based on a small number of new cancer studies identified since the 2016 PFOS HA, EPA concludes that the available cancer data for PFOS indicate a ‘suggestive’ categorization which is unchanged from the categorization identified in the 2016 HA. Does the panel agree that the new studies do not change the designation? If yes, is the rationale clearly described? If no, please provide an explanation for arriving at a different conclusion.

I support EPA’s decision to update PFOA as a ‘likely carcinogen’ but disagree with EPA regarding PFOS, which should also be updated as a ‘likely carcinogen’. California’s OEHHA recently conducted a systematic review in which they structured their decision making based on the 10 key characteristics of cancer (CalEPA 2021; Smith et al. 2016) and have proposed listing PFOS and its salts and transformation and degradation precursors as carcinogenic under Prop65. To summarize the major differences, OEHHA, like EPA, concluded that the epidemiological data on PFOS and cancer is still inconclusive, however OEHHA came to a different conclusion than EPA regarding the strength and conclusions of the rat chronic cancer study from Butenhoff et al. (2012) (Butenhoff et al. 2012). Whereas EPA stated there were no clear dose-related responses from the study, OEHHA stated:

“Significant tumor findings are as follows:

6.2.1 Liver tumors

- In PFOS-treated male rats, the incidence of hepatocellular adenoma was significantly increased in the high-dose (20 Parts per million) group by pairwise comparison with controls, with a significant dose-related trend.*
- In PFOS-treated female rats, the incidences of hepatocellular adenoma and adenoma or carcinoma combined were significantly increased in the high-dose (20 Parts per million) group by pairwise comparison with controls, with significant dose-related trends. One rare hepatocellular carcinoma was observed in the 20 Parts per million group.*

6.2.2 Pancreatic tumors

- In PFOS-treated male rats, the incidence of islet cell carcinoma was significantly increased with a statistically significant dose-related trend.*

6.2.3 Thyroid tumors

- In PFOS-treated male rats, the incidence of thyroid gland follicular cell adenoma was significantly increased by pairwise comparison with controls in the “20 Parts per million recovery” group, that is, exposure for 12 months followed by 12 months on the basal diet.*
- In PFOS-treated female rats, two rare thyroid gland follicular cell adenomas and one rare follicular cell carcinoma were observed in the 5 Parts per million group, and one rare follicular cell adenoma was observed in the 20 Parts per million group. Additionally, one rare follicular cell adenoma was observed in the “20 Parts per million recovery” group.*

6.2.4 Mammary tumors

- In PFOS-treated female rats, the incidence of mammary fibroadenoma was significantly increased in the low-dose (0.5 Parts per million) group by pairwise comparison with controls” (CalEPA 2021).*

Further, OEHHA considered a tumor promoting study conducted in trout, an animal model chosen for its similarity to human insensitivity to peroxisome proliferation (Benninghoff et al. 2012; CalEPA 2021). EPA did not review this study because it did not meet the PECO criteria,

and even though it could be considered a study with important supplemental information, it was not discussed (US EPA 2021e).

Another important difference is that OEHHA made use of the existing *in vitro* and mechanistic data which provided additional evidence that PFOS impacts seven of the ten key characteristics of cancer, whereas EPA stated, “Additional analysis on the mechanistic actions of PFOS on cancer health outcomes is pending and is expected to be completed after the EPA SAB review” (US EPA 2021e). It is unclear why the EPA is presenting an unfinished analysis to the SAB. Even before the recent proposed listing of PFOS as a carcinogen under Prop65, OEHHA had derived both cancer and non-cancer based reference levels for PFOS (also, based on the Butenhoff et al., 2012 study) (OEHHA 2019) and incorporated this into the derivation on Public Health Goals (OEHHA 2021b). Other authoritative bodies, including IARC and the Report on Carcinogens support using the key characteristics of cancer framework to evaluate mechanistic data when evaluating a chemical as a potential carcinogen (NTP 2015; Samet et al. 2020).

Epidemiological Study RfD Derivation

4. EPA has evaluated and applied where appropriate uncertainty factors to account for intraspecies variability (UFH), interspecies differences (UFA), database limitations (UFD), duration (UFS), and LOAEL-to-NOAEL extrapolation (UFL) for PFOA and PFOS.

A. Has uncertainty been adequately accounted for in the derivation of the RfDs? Please describe and provide suggestions, if needed.

B. Does the provided scientific rationale support the application of the selected uncertainty factors? Please explain.

An interesting discussion occurred during the public meeting on December 16, 2021, in which it was suggested that an additional uncertainty factor could be applied to account for the evidence that PFOA and PFOS are frequently detected together in drinking water. One way to account for this that was suggested during the meeting is to apply a mixture assessment factor. The use of such an approach deserves additional consideration given the large number of PFAS that may co-occur in drinking water.

Relative Source Contribution

1. EPA applies a Relative Source Contribution (RSC) when calculating the MCLG to provide a margin of safety that an individual’s total exposure from a contaminant does not exceed the RfD. The RSC is the portion of an exposure for an individual in the general U.S. population estimated to equal the RfD that is attributed to drinking water; the remainder of the exposure equal to the RfD is allocated to other potential sources. Based on the physical properties, detected levels, and available exposure information, there are significant potential sources other than drinking water ingestion for PFOA and PFOS; however, information is not available to quantitatively characterize exposure from these different sources. EPA followed Agency guidance on how to derive an RSC (U.S. EPA, 2000; available online at: <https://www.epa.gov/sites/default/files/2018->

[10/documents/methodology-wqc-protection-hh-2000.pdf](https://www.epa.gov/10/documents/methodology-wqc-protection-hh-2000.pdf)) and recommends an RSC of 20 percent (0.20) for PFOA and PFOS. This RSC is the same as what was used in the 2016 HAs for PFOA and PFOS.

A. Are you aware of additional relevant exposure data that EPA should consider in developing the RSCs for PFOA and PFOS? If so, please provide citations.

B. Please provide comment on whether the recommended RSC of 20 percent (0.20) for PFOA and PFOS is adequately supported and clearly described.

Overall, I support the use of the 20% RSC for drinking water, as it is the most health protective choice. It is surprising however that the documents do not discuss which drinking water intake assumptions would be the most appropriate to use. The 2016 Lifetime Health Assessments used an adult drinking water assumption, that was not protective of pregnant women, children, or infants, all of which are both more vulnerable to the health impacts associated with PFAS exposure and also more susceptible given that they consume more water on a per body weight basis. I would recommend that EPA address the drinking water intake assumptions in these documents.

Charge Questions for SAB on EPA's Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)

Overall charge: EPA is seeking SAB comment on whether the framework and illustrative examples provided in the document are scientifically supported, clearly described, and informative for assessing potential health risk(s) associated with exposure to mixtures of PFAS.

Charge questions

1. The component-based mixtures approaches presented in the framework are based on dose addition. Traditionally, an assumption of dose addition for a mixture is based on components sharing a common mode of action (MOA) for a given health effect. However, EPA's supplementary guidance (EPA, 2000) states: "The common mode-of-action (MOA) assumption can be met using a surrogate of toxicological similarity, but for specific conditions (endpoint, route, duration)." This suggests that although the common MOA metric for application of dose addition is optimal, there is flexibility in the level of biological organization at which "similarity" can be determined among mixture components. As an emerging chemical class, MOA data is limited or not available for many PFAS. For purposes of a component-based evaluation of mixtures additivity for PFAS, EPA assumes similarity at the level of toxicity endpoint/health effect rather than MOA.

A. Please comment on the appropriateness of this approach for a component-based mixture evaluation of PFAS under an assumption of dose additivity.

The choice to base component based evaluation of PFAS mixtures on similar toxicity rather than a known mode of action is sound. Though the mode of action is not elucidated for PFAS health effects, it is well known that many PFAS act on the same organ and tissue system.

2. Section 4.3 (Hazard Index; HI) of the framework document demonstrates the application of a component-based mixture approach, based on dose addition, using available oral reference doses from completed EPA human health assessments, and hypothetical exposure information. The example calculations presented are primarily focused on four PFAS with finalized EPA Human Health Assessments: perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorobutane sulfonic acid (PFBS), and hexafluoropropylene oxide (HFPO) dimer acid and HFPO dimer acid ammonium salt (referred to as “GenX chemicals”).

A. Please provide specific feedback on whether the HI approach is a reasonable methodology for indicating potential risk associated with mixtures of PFAS. If not, please provide an alternative.

B. Please provide specific feedback on whether the proposed HI methodologies in the framework are scientifically supported for PFAS mixture risk assessment.

Given that we know that PFAS often occur in the environment in mixtures, that there are potentially many thousands of PFAS, that current US EPA validated methods only measure a small fraction of the possible PFAS and that many PFAS act on the same biological target, it would be prudent to set the HI cut-off at 0.1 rather than 1.0 in order to better account for the many unknowns.

Charge Questions for SAB on CVD Methodology

Introduction

To fulfill the Health Risk Reduction and Cost Analysis (HRRCA) requirements under Safe Drinking Water Act, EPA is developing a benefit-cost analysis and other related rule analyses to inform consideration of regulatory alternatives. According to the *Proposed Approaches to the Derivation of Draft Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water, currently under concurrent SAB review*, current epidemiologic literature supports positive associations between PFOA and PFOS exposure and total cholesterol. EPA is developing national-level benefits estimates for avoided cardiovascular disease risk as a result of PFOA and PFOS exposure reduction via drinking water. The draft document *Analysis of Avoided Cardiovascular Disease Risk from Reduced PFOA and PFOS Exposure* presents a methodology that could be used to determine the avoided cases of cardiovascular disease events (e.g., heart attack, stroke, death from coronary heart disease). EPA intends to use this methodology to quantify the cardiovascular risk-reduction benefits for the population served by public water systems PWSs expected to take action to comply with a PFAS drinking water regulation.

I would like to encourage EPA to be more transparent about which specific health impacts will be investigated using this or a similar methodology. As PFAS are systemic toxicants, will EPA perform similar analyses for all of the health effects for which a POD was derived?

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