

Charge Questions for SAB Review of the Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water

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.

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?
2. Elevation of liver serum biomarkers in humans is frequently used as 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.
3. Does the SAB panel agree with EPA's rationale for not considering the ALT endpoint reported in the epidemiological studies for the derivation of a POD for the liver health effects? Please provide your justification and if you suggest that EPA consider this endpoint for POD derivation, please provide your recommendations for a modeling approach.
 - A. Are you aware of additional studies that support the ALT levels as markers of adverse liver effects? Please provide citations.
 - B. Are there other adverse liver endpoints identified in the epidemiological literature that need to be considered?

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.
2. Cancer Slope Quantification: EPA used the Shearer et al., 2021 epidemiological study to quantify a cancer slope factor using peak exposure for PFOA. Has EPA adequately justified the use of this study and peak exposure for the quantification of a cancer slope factor for PFOA? If no, please describe alternate approaches that SAB recommends.

Toxicokinetic Models

- 1. Human model –
 - A. For endpoints observed in adults, EPA used a steady-state approach to calculate the HED, which assumes a relatively constant exposure and clearance during adulthood. Please comment on this method of HED calculation. Are there alternative approaches that EPA should consider? If so, please describe the rationale for recommending this approach(es).
 - B. Two key parameters are the half-life and volume of distribution, which were used to calculate clearance. Half-life and volume of distribution were assumed to be constant across sex and age groups because of a lack of strong quantitative data to parametrize changes across sex and age. Please comment on the strengths and weakness of the use of this assumption and the choice of these parameters by the EPA. Please describe the rationale for alternative recommended approaches. For endpoints observed in human neonates or children, EPA used a one-compartment TK model to simulate dosimetry during pregnancy and a two-compartment TK model (one-compartment models for the mother and the child) to simulate dosimetry during lactation, to calculate the HED for each POD. Please comment on the strengths and weaknesses of this choice of model structure for the task of predicting dosimetry in the human fetus and child compared to dosimetry in mice and rats in the similar lifestages. Please provide the rationale for any alternative recommended approaches.
 - C. The key chemical-specific parameters that describe the transfer of the chemical from the mother to the child during gestation and lactation are the maternal to fetal serum ratio and the ratio of maternal serum to milk PFOA/S concentration. These ratios were assumed to be constant during gestation and lactation,

respectively. Another important parameter is the rate of milk ingestion, which is chemical-independent and varies throughout lactation. Please comment on the strengths and weaknesses of the choice of parameters for fetal to maternal partitioning and partitioning into breastmilk, as well as the choice for lactation rate. Please also comment on the choice to assume that fetal to maternal partitioning and partitioning to breastmilk did not vary in time. Please describe whether there are other methods you would recommend to account for these changes over time and across development.

2. Animal Model –

- A. After a review of the available toxicokinetic models for PFOA/S predictions in laboratory animals, EPA selected the Wambaugh et al. (2013) model because it was parametrized using all species of interest, demonstrated good agreement with training and test datasets, and used a single, biologically motivated, model structure across all species. Does the panel agree with selecting this model? If not, please describe the rationale for alternative recommended approaches for the calculation of the internal dose metrics in adult animals.
- B. The animal model parameters were obtained through a Bayesian inference parameterization which produced wide credible intervals for some parameter values, but relatively tight credible intervals for the predicted serum concentration. Does the panel agree with using the median values of the estimated animal parameter distributions for prediction of serum concentration and internal dose metrics?
- C. Based on visual inspection of model predictions to the calibration datasets, EPA utilized sex-independent parameters for PFOS. The male-specific parameters were used for all rat-specific PFOS predictions including predictions in pregnant and nursing dams and the female-specific parameters were used for all mouse-specific PFOS predictions because the parameter values obtained from fitting the female-specific rat data and male-specific mouse data were not consistent with the overall TK parameters for PFOS and produced poor fits to the training and test datasets. Does the panel agree with this approach and justification for this assumption for PFOS? If not, please describe other approaches that could be considered?
- D. EPA assumed a one compartment model for the developing infant based on the lack of infant-specific toxicokinetic data from rats and mice. This model utilizes averages of half-life and volume of distribution from the literature coupled with physiologically relevant lactational parameters for pup nursing. Does the panel agree with the decision to use this model structure for infant animals? If not, please provide data on infant-specific changes during the animal lactational-period that could be used to account for toxicokinetic differences between the adult and infant rats and mice.

- E. Several parameters dictate the transfer of chemical from the mother to her pup. Does the panel agree with the selection of these parameters for the animal model? If not, please provide your justification and alternative parameters.
- F. For neonatal animals, EPA assumed no sex differences in clearance in neonatal animals based on the lack of identification of sex-dependent differences in PFOA/S toxicokinetics from the available data. Does the panel agree with this assumption? If not, please provide your justification and available data on sex differences in neonatal rats.

Epidemiological Study RfD Derivation

1. EPA evaluated potential confounding as part of their study quality evaluation of the epidemiological studies and selected only 'medium' and 'high' quality studies for POD derivation. Have the epidemiological studies that were selected for dose-response modeling sufficiently addressed confounding? If not, are there key additional analyses that could be performed to further address the potential confounding of PFAS exposures in these studies?
2. Studies of developmental immune health outcomes (Grandjean et al., 2012 [HERO ID: 1248827]; Grandjean et al. 2017 [HERO ID: 3858518]; Grandjean et al., 2017 [HERO ID: 4239492]; and Budtz-Jorgensen and Grandjean, 2018 [HERO ID: 5083631]) after PFOA/S exposure identified associations with very low doses of either PFOA or PFOS with developmental immune effects. The RfD for this outcome was selected as the critical effect because it was the lowest among the candidate RfDs for PFOA or PFOS and can result in severe illness. Does the panel agree with the selection of the critical study and critical effect for the derivation of chronic RfDs for PFOA and PFOS?
 - A. If so, please explain your justification.
 - B. If not, please provide your rationale and detail an alternative critical study and/or critical effect you would select to support the derivation of chronic RfDs.
 - C. Are any additional analyses or rationales needed to increase the confidence in the chronic RfDs for PFOA and PFOS?
3. The health outcomes identified in the critical studies were decreased antibody response, specifically in serum anti-tetanus and anti-diphtheria, in children after vaccination (Grandjean et al., 2012 [HERO ID: 1248827]; Grandjean et al. 2017 [HERO ID: 3858518]; Grandjean et al., 2017 [HERO ID: 4239492]; and Budtz-Jorgensen and Grandjean, 2018 [HERO ID: 5083631]). This health outcome represents an increased susceptibility to a disease that can cause very severe symptoms, including lethality. Furthermore, children who are immunocompromised may mount a lower antibody response and in turn, be more susceptible to contracting the disease, if exposed than healthy children. Because this health outcome has the potential for severe illness and was assessed in children (i.e., EPA guidelines [US EPA, 1991] support a 5% BMR for

developmental effects), a benchmark response (BMR) of 5% was selected for benchmark dose modeling. While some clinical findings are available, the clinical relevance of a 5% decrease in antibody response is not clear. Given the need to protect sensitive subpopulations (e.g., children, individuals with pre-existing conditions) and the available clinical data (i.e., antibody response clinical level), does the SAB support the 5% BMR selection for modeling to identify the POD? If not, please recommend the BMR level and a scientific rationale for an alternative selection.

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.

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>) 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.

Citations

Boone, L; Meyer, D; Cusick, P; Ennulat, D; Bolliger, AP; Everds, N; Meador, V; Elliott, G; Honor, D; Bounous, D; Jordan, H. (2005). Selection and interpretation of clinical pathology indicators of hepatic injury in preclinical studies [Review]. Vet Clin Pathol 34: 182-188.

Budtz-Jørgensen, E; Grandjean, P. (2018). Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity. PLoS ONE 13: e0205388.

Grandjean, P; Andersen, EW; Budtz-Jørgensen, E; Nielsen, F; Mølbak, K; Weihe, P; Heilmann, C. (2012). Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 307: 391-397.

Grandjean, P; Heilmann, C; Weihe, P; Nielsen, F; Mogensen, UB; Budtz-Jørgensen, E. (2017). Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. Environ Health Perspect 125: 077018.

Grandjean, P; Heilmann, C; Weihe, P; Nielsen, F; Mogensen, UB; Timmermann, A; Budtz-Jørgensen, E. (2017). Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. J Immunotoxicol 14: 188-195.

Shearer, JJ; Callahan, CL; Calafat, AM; Huang, WY; Jones, RR; Sabbisetti, VS; Freedman, ND; Sampson, JN; Silverman, DT; Purdue, MP; Hofmann, JN. (2021). Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma. J Natl Cancer Inst 113: 580-587.

U.S. EPA. (1991). Guidelines for Developmental Toxicity Risk Assessment. EPA, Risk Assessment Forum. Federal Register, Dec. 5, 1991, 56(234):63798–63826.

U.S. EPA. (2000). Methodology for deriving ambient water quality criteria for the protection of human health (2000). (EPA/822/B-00/004). Washington, DC: U.S. Environmental Protection Agency, Office of Water.

U.S. EPA. (2002). A review of the reference dose and reference concentration processes. (EPA630P02002F). Washington, DC.

U.S. EPA. (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA630P03001B). Washington, DC.

Charge Questions for SAB

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

Introduction

Per- and polyfluoroalkyl substances (PFAS) present many unique challenges from a risk management perspective due to the large number (1000's) and structural diversity of members in this chemical class, limitations in available human health and exposure information, and the spatial and temporal variability of their presence in drinking water and other environmental media. To inform various decision contexts in addressing PFAS contamination, EPA has developed a draft *Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS* to illustrate the practical application of EPA chemical mixtures approaches and methods^{1,2} for two or more PFAS co-occurring in environmental media. Specifically, this document describes an approach for providing a tiered, flexible, data-driven framework that facilitates practical component-based mixtures evaluation of two or more PFAS under an assumption of dose additivity. While this framework is being developed to inform the National Primary Drinking Water Regulation for PFAS, it is not intended to be media-specific in practical applications.

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.
 - B. If common toxicity endpoint/health effect is not considered an optimal similarity domain for those PFAS with limited or no available MOA-type data, please provide specific alternative methodologies for integrating such chemicals into a component-based mixture evaluation(s).

1. EPA (Environmental Protection Agency). 1986. *Guidelines for the Health Risk Assessment of Chemical Mixtures*. EPA/630/R-98/002. EPA, Risk Assessment Forum, Washington, DC.
2. EPA (Environmental Protection Agency). 2000. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*. EPA/630/R-00/002. EPA, Risk Assessment Forum, Washington, DC.

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.
3. Section 4.4 (Relative Potency Factor; RPF) of the framework document demonstrates the application of a component-based mixture approach, based on dose addition, using available dose-response information (i.e., points-of-departure) from completed EPA human health assessments, and hypothetical exposure information. The example RPFs and corresponding Index Chemical Equivalent Concentration (ICEC) calculations presented are primarily focused on four PFAS with finalized EPA Human Health Assessments: PFOA, PFOS, PFBS, and HFPO dimer acid and GenX chemicals.
 - A. Please provide specific feedback on whether the RPF approach is a reasonable methodology for estimating risk associated with mixtures of PFAS. If not, please provide an alternative.
 - B. Please provide specific feedback on whether the proposed RPF methodology in the framework is scientifically supported for PFAS mixture risk assessment.
4. Section 4.5 (Mixture BMD) of the framework document demonstrates the application of a component-based mixture approach using established EPA dose-response modeling (i.e., benchmark dose; BMD) of hypothetical PFAS dose-response data, and hypothetical exposure information.
 - A. Please provide specific feedback on whether the Mixture BMD approach is a reasonable methodology for estimating what is in essence a mixture-based point-of-departure. If not, please provide an alternative.
 - B. Please provide specific feedback on whether the proposed Mixture BMD methodology in the framework is scientifically supported for PFAS mixture risk assessment.

1. EPA (Environmental Protection Agency). 1986. *Guidelines for the Health Risk Assessment of Chemical Mixtures*. EPA/630/R-98/002. EPA, Risk Assessment Forum, Washington, DC.
2. EPA (Environmental Protection Agency). 2000. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*. EPA/630/R-00/002. EPA, Risk Assessment Forum, Washington, DC.

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.

EPA is seeking input from SAB on the proposed methodology for estimating the avoided cases of cardiovascular disease (CVD) that result from reductions of PFOA and PFOS in drinking water. Evaluation of CVD impacts involves three main steps:

- 1) Estimate the changes in serum PFOA and PFOS levels that result from changes in drinking water concentrations with pharmacokinetic (PK) model¹;
- 2) Estimate the changes in total cholesterol that result from changes in PFOA and PFOS serum concentrations using dose-response functions for PFOA/PFOS; and
- 3) Estimate the change in probability of hard CVD events that result from changes in total cholesterol to estimate CVD event incidence in baseline and policy scenarios.

Overall charge: EPA is seeking SAB comment on the extent to which the approach to estimating reductions in CVD risk associated with reductions in exposure to PFOA and PFOS in drinking water is scientifically supported and clearly described.

Charge Questions

1. Section 4.2 presents EPA's meta-analysis for the total cholesterol dose-response function.
 - A. Please provide specific feedback on the extent to which the study selection criteria, the identified studies, and the methodological approach of the meta-analysis are complete and capture up to date scientific literature.

¹ EPA describes the human PK model within [OST's MCLG document] and requests SAB comments on the PK model to be provided in response to that document.

B. To inform the CVD risk reduction analysis for those ages 40-89 using the ASCVD risk model, EPA used a meta-analysis approach for the total cholesterol dose-response function. Please provide specific feedback on the extent to which this approach is reasonable for this application, or whether using a single dose-response study (e.g. Dong et al., 2019) selected in the analysis of cholesterol impacts in the *Proposed Approaches for Deriving Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water* would add additional strengths for the CVD risk reduction application.

2. Section 5.1 presents EPA's life table approach methodology.

A. Please comment on the extent to which this analysis is scientifically supported and clearly described. To the extent improvements are suggested, please provide specific changes that are implementable in a U.S. national-level benefits analysis with readily available data.

3. Section 5.2 presents EPA's application of the atherosclerotic cardiovascular disease (ASCVD) risk model used to estimate the probability of hard CVD events corresponding to total cholesterol changes.

A. Please comment on the scientific validity of the ASCVD model application for estimating the probability of first time CVD events in various sub-populations and the extent to which it is clearly described.

B. Please comment on whether EPA's approach and assumption, of a uniform first CVD event hazard distribution over the 10-year period, is sufficiently robust given current data sources and literature. If additional distributional sources of information are suggested, please provide specific citations/sources for EPA's consideration.

C. Please comment on the scientific validity of using the ASCVD risk model for estimating reduced CVD risk stemming from changes in total cholesterol in response to reducing exposure to PFOA and PFOS in drinking water.

4. Section 7 and Appendix A describe the limitations and uncertainties of the CVD risk reduction analysis. Has EPA clearly described the individual contributions of the sources of uncertainty?