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Quality Review Comments from SAB Members on the SAB Draft Report: *Review of EPA’s Analyses to Support EPA’s National Primary Drinking Water Rulemaking for PFAS*

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As of July 17, 2022**

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Comments from Lead Reviewers

Comments from Dr. Marjorie Aelion

Review of EPA's Analysis to Support EPA's National Primary Drinking Water Rulemaking for PFAS

In your comments, please address the four quality review questions below from the vantage point of your own experience:

1) Were the charge questions to the Committee adequately addressed?

Yes. The draft report is highly detailed and addresses the charge questions posed by EPA. It provides in-depth responses to the EPA queries, and an extensive list of references in support of all conclusions and recommendations. These can be accessed by EPA for additional detail.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I found no technical errors of omissions in the draft report.

3) Is the draft report clear and logical?

Yes, the draft report is clear and logical. A few of the suggestions were repeated several times in the document, for example the Panel concluded that the decision to exclude literature published within the timeframe of the development of the 2016 health effects support document (HESD; U.S.EPA, 2016) in the current literature search was unjustified. This comment occurred in different points of the report in response to charge questions so its repetition was justified.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions drawn or recommendations provided are supported by the body of the draft report. As stated in response to Question 1, the draft report is highly detailed and provides in-depth responses to the EPA queries. It also provides extensive list of references in support of all conclusions and recommendations.

Comments from Dr. Mark Borsuk

Quality Review Questions for the SAB PFAS report

1. Were the charge questions to the Panel adequately addressed?

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The charge questions were generally well addressed by the Panel, with one exception. Charge Question #2B asks that the SAB panel “provide your recommendations for modeling approaches” (for the consideration of the ALT endpoint required for the derivation of a POD for the liver health effects). Although the panel does recommend considering the ALT endpoint, they do not provide any recommendations for modeling approaches.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

There were no technical errors or omissions, although I did find a few typos, grammatical errors, and possible word omissions, which I can send along separately. Perhaps most notably, I found the following wording on page 107 confusing: “Overall, the Panel recommends more discussion as to the rationale for selecting this particular endpoint for risk reduction analysis (e.g., strengthening of the hazard conclusion with respect to PFOA or PFOS, availability of dose-response data from which to derive a dose-response function or risk-specific dose estimates, strengthening of data connecting changes in biomarker to changes in morbidity or mortality, and availability of data for monetizing benefits).” Why is the word “strengthening of the” used and not “stronger”? Isn’t the intent of this sentence to justify the endpoint, not to improve the endpoint? This same strange wording is used again on page 108 in the second recommendation.

3. Is the draft report clear and logical?

The draft report is generally clear and logical. One point made on page 4 of the cover letter and in section was less clear. The SAB panel suggests that the phrase “external peer review” be “broadened to recommend the need for scientific input and review in general.” I am unclear what the intended by this recommendation. Is it to suggest that review does not need to be “external” or is it to suggest that the review must be “scientific”, or perhaps to point out that there are other forms of “input” beyond peer review. I suggest that the panel provide more detail on their intention with this recommendation.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions and recommendations are well supported by the body of the draft report.

Comments from Dr. Dominique van der Mensbrugghe

1. To the extent of my limited knowledge in this area, I believe that the charge questions were adequately addressed by the Panel.
2. Overall, I did not identify any errors or omissions in the draft report. The draft report perhaps could have highlighted in more places the heterogeneous impacts of PFAS on different segments of the population—by age, race, socio-economic background, etc.
3. Though a difficult read in many places due to the technical nature of the issues addressed, the draft report is largely clear and logical (and thorough).
4. The conclusions and recommendations are supported by the draft report.

Some additional comments on the cardiovascular disease (CVD) report:

- The draft report could perhaps take a stronger position on the justification for the CVD analysis. It clearly states that “elevated serum cholesterol is one of the better-established effects of PFAS

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exposure in humans.” Is the panel suggesting that EPA re-evaluate the evidence for not having the ability to develop a CVD-based RfD, or does the panel believe the focus should be on the PFAS link to cholesterol levels and not to CVD? Presumably if there is a PFAS to cholesterol to CVD link, one could undertake a detailed benefit-cost analysis that would show the relevant trade-offs, does this not lead to an RfD (with some probability distribution)?

- The draft report highlights some of the challenges in incorporating more population heterogeneity in the analysis—for example the risk of CVD changes with age, and that the ASCVD model has limited parameterization across age and sub-populations. The heterogenous response and the desire to address it could be stressed more broadly.

Comments from Dr. June Weintraub

1. Were the charge questions to the Panel adequately addressed?

The report “Review of EPA’s Analysis to Support EPA’s National Primary Drinking Water Rulemaking for PFAS” was developed in response to the EPA’s request that the SAB review four draft documents that were written in support of an upcoming rulemaking for PFAS. The report is extensive and comprehensive—all the charge questions and sub-questions were adequately addressed.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not identify any serious technical errors or significant omissions, although my technical expertise on some of the topics covered in this report may be limited.

I noted a few typos and grammatical errors:

Page 3, Line 23: change the word “use” to “used”

Page 3, Line 36: suggest replacing the word “contends” with the word “states” Throughout: I believe in most cases “EPA” should be “the EPA”

3. Is the draft report clear and logical?

The draft report is well-written and logically organized, with the charge questions preceding each section of the text. The draft report has many subsections, and could benefit from a few changes to better orient the reader. For example, it would be helpful to change the sub headers for the first charge to match the sub headers that are used in the EPA Draft MCLG document. That is, instead of headers on the left-hand column below, use the ones on the righthand column to better orient the reader to the sections being referenced:

Headers in SAB Panel Report	Headers in EPA Draft MCLG documents
Problem formulation and protocol development	Problem Formulation and Criteria
Evidence Identification	Literature Search Strategy and Screening Process
Evidence Evaluation	Study Evaluation
Data Extraction	Data Extraction
Evidence Synthesis	Evidence Synthesis

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As another example, when Charge Questions are split into A, B and C sub-questions, it would be helpful to put the main number in front of the letter (e.g. change “B.” to “3.B.” on line 22 of page 37. It also appears that the lettering may be off, as there is also a part B of Section 3 on page 41.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations are supported by the information and evidence presented in this draft report.

Comments from other SAB Members

Comments from Dr. Joseph Arvai

1. Were the charge questions to the Panel adequately addressed?

In my opinion, yes.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Many of the concepts and recommendations discussed in the SAB PFAS report fall well outside of my areas of expertise. However, in my view, the report was clearly written and thoughtfully contextualized. Thus, to the best of my ability, I did not detect any (a) technical errors or (b) omissions or (c) issues that required additional attention in the draft report.

3. Is the draft report clear and logical?

In my opinion, yes.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

In my opinion, yes.

Comments from Dr. Roland Benke

PFAS responses to quality review questions

1. Yes, but one question follows. EPA used a steady-state approach to calculate the HED, which assumes a relatively constant exposure and clearance during adulthood. Regarding the response to Charge Question 4 for the human toxicokinetic model, identification of its highly empirical nature and limitation for mixtures is appreciated. No alternative model was suggested for the animal model. In light of specific suggestions provided for the human model, can a

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remark be added to the response if any of the suggestions are advantageous for addressing mixtures?

2. None found.

3. Yes. It is acceptable. However, editorial suggestions were provided separately to improve flow.

5. Yes. Well done!

Additional editorial comments provided separately.

Comments from Dr. Alison Cullen

1. Were the charge questions to the Panel adequately addressed?

The charge questions were addressed with clarity and comprehensive descriptions of concerns.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

None that I found. The report is very thorough. Despite using systematic review, the panel identified key publications and data that were missed. Inclusion of these studies will strengthen the draft MCLG document.

3. Is the draft report clear and logical?

The report is clearly written and the organization is logical. The panel and staff are to be commended for a great job.

Minor points:

The letter to Administrator Regan says “EPA should focus on those health outcomes that have been concluded to have the strongest evidence, including the liver, immune system, serum lipids, fetal growth, and cancer.” I note that “liver, immune system, serum lipids, fetal growth” are not health outcomes. Perhaps these should be listed as “... liver disease, immune system dysfunction, serum lipid aberration, impaired fetal growth, and cancer.” Also, in the Administrator letter “BMD” is not defined at its first use. “RSC” and “ASCVD” are not defined.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

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There were many specific and actionable recommendations. These were consistent with the concerns raised and were well supported by the text.

Comments from Dr. John Guckenheimer

1. Were the charge questions to the Panel adequately addressed?

Yes

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No

3. Is the draft report clear and logical?

Yes, but the SAB reviews are narrow in scope and directed primarily to the EPA authors of their reports.

The PFAS report is a lengthy review of an issue that has significant public impact and few definitive scientific results. The logic for establishing goals for maximum acceptable levels of PFAS in drinking water is based partly upon its ubiquity and persistence in the environment. These levels are determined by analysis of epidemiological data from communities with high levels of exposure and extrapolation from animal studies. Instead of clearly explaining how a Maximum Contaminant Goal Level is derived from these data, both the EPA draft and the SAB review focus upon procedural matters like how literature surveys were conducted and described. Measuring the transport of PFAS in the environment and the health effects of the thousands of PFAS compounds are sufficiently incomplete that the SAB could be helpful by insisting upon a transparent description of the science used by the EPA to set MCGL beyond the formulation of protocols for PFAS research. The SAB Quality Review should be based upon a broader perspective than individual responses to the lengthy charge questions.

Here is an example of an issue that is relevant to MCGL but not part of the EPA charge for the SAB review. The underlying question is whether PFAS is a significant factor in contributing to the obesity epidemic in this country and worldwide. Some studies (e.g., Liu, G; Dhana, K; Furtado, JD; Rood, J; Zong, G; Liang, L; Qi, L; Bray, GA; Dejonge, L; Coull, B; Grandjean, P; Sun, Q. (2018). Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: A prospective study. PLoS Med 15: e1002502.) suggest that PFAS affects our ability to control weight. See section 3.3.7 of the EPA Draft Report. While the evidence this association is hardly clear, obesity has become a major public health concern over several decades. If low concentrations of PFAS in drinking water at levels below the recommended MCGL contribute to obesity, then the MCGL should be reduced. This should be discussed in the EPA report.

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4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Angela Leung

1. Were the charge questions to the Panel adequately addressed? YES
2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report? NO
3. Is the draft report clear and logical? YES
4. Are the conclusions drawn or recommendations provided supported by the body of the draft report? YES

Comments from Dr. John Morris

My comments on the SAB PFAS report are structured around the four quality review questions that were provided in the Chair's memo.

1) The PFAS report more than adequately addressed the charge questions brought forward by EPA. The review committee is to be complemented for preparing a thorough, thoughtful, and carefully worded review report that fully addresses each charge question. Moreover, this detailed review report is replete with additional information and literature citations (e.g. for the use of ALT, p30; dose-response analysis for serum lipids, p24, or TK modeling, p49, etc.) to support their conclusions and which should serve to guide the response of EPA to the review. The review report also clearly indicates issues for which the committee received consensus versus those which it did not, providing assurance that the report details non-biased and factual substantiation for their responses to the provided charge questions. Many responses to the charge questions raised significant substantive concerns; it is particularly important that concerns of this magnitude be carefully substantiated. This high level of substantiation was achieved.

2) I am aware of no technical errors or omission in the review report.

3) The review report is clear and logical. As a very minor editorial point, the text of most sections of the review report is very careful to avoid enumerating specific recommended actions in the body of the text for each section and only provide those in the recommendation sections. However, in the response to charge question #2A, there appears to be some specific action recommendations in the body of the text (e.g. p20, line 6; p21, line4 and line 15; p23, line 38).

4). In the response to every charge question the actions recommended in the review report are fully and clearly supported by the body of text for that question. The recommendations highlighted in the draft cover letter clearly follow from the subsequent report and are clearly

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presented with appropriate detail. The committee is to be complemented for the thoughtfulness, clarity and tactfully worded text that they prepared.

In the latter portions of the review report (p 56 on dealing with RfD derivation and uncertainty factor approaches) the concerns raised are for the most part reflective of the need for greater clarity rather than substantive concerns and outright fundamental disagreement with the conclusions and processes described in the EPA document. The recommendations followed clearly and directly for the body of text and the tone of the recommendations is fully consistent with the magnitude of the concerns that are expressed.

For the earlier portion of the review report, I am a little torn relative to the recommendations themselves and the tone with which they are written compared to the magnitude of the issues identified in the body of the text. While the committee is to be complemented by the tact with which the concerns are raised, it might be possible that the text is so tactfully worded in the recommendation sections that the severity of concern is diminished. The body of the text used very strong language, for example: “major deficiency” (p5, line 32); “deficient” p6, line 27; “unjustified” p17, line 19; “not clear or supportable” p7, line 29; the “Panel does not agree with EPA’s rationale..” (p26, line 36). (Numerous other examples could be provided.) Might the recommendation sections be more strongly worded to reflect the magnitude of concern?

I also wonder if, perhaps, the fundamental recommendation might better be for the EPA to redo the systematic review properly and redo the report? In essence, it appears to my reading, that the text provides devastating criticisms and enumerates glaring deficiencies in the systematic review process, and also lists several critical references that were missed. Is the methodology so flawed it calls into question the validity of the subsequent report and its conclusions? Yes, the review committee provided numerous additional references for consideration and detailed alternate conclusions, but is the use of additional references provided by ad hoc reviewers really true to the goal of an *a priori* defined systematic review process? Perhaps would be sufficient (if true) to include in the review report a statement that while significant concerns were raised relative to the systematic review they do not appear to invalidate the overall conclusions of the document. I don’t know the answer to these questions, but I wonder if it might be worthy of some discussion during our conference call.

Section II – Mixtures Approaches

1. The charge questions were thoroughly addressed. The inclusion of additional literature citations and specific examples to demonstrate the reviewers’ logic represent strengths of the review.
2. I know of no technical errors or omissions.

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3. The report was well written and was clear and logical. One minor point deals with the issue of literature that was not cited relative to additivity (p 90). It is unclear whether the identified non-cited literature was captured in the EPA literature search and then discounted (if so, why?) versus not being captured in the literature search (if so, why?). Inclusion of this information would enhance clarity. In this regard, I note that such information is explicitly provided in the CVD risk reduction section (P109, lines 37-38).

4. Fundamentally the review indicated agreement with the approaches recommended by EPA for general additivity based on endpoint, use of RPF, HI/TOSHI, and mixture BMD approaches, etc.; the text indicates the need for additional clarity and transparency not total revision. The draft report text provides strong support for the conclusions that were drawn.

I raise one question relative to the review's conclusions and support of same. I concur with the expressed view that something broader than "external peer review" would be appropriate. Given the great expansion in number of journals and the current existence of junk journals I wonder if it might be appropriate to draw attention to the issue that the mere existence of a publication in a "peer reviewed" journal is not sufficient to infer quality.

Slightly unclear are the recommendations relative to the mathematical approach to dose additivity. The text has a lengthy section highlighting that the two approaches are fundamentally the same and, thus, the differences of those approaches shouldn't be overemphasized (p 101-102). Despite the lengthy text there is no specific recommendation regarding this issue, which is somewhat confusing.

Section III – Benefits from CVD reduction

1. The charge questions are more than adequately addressed. As in other sections of the review inclusion of multiple literature citations represents a strength.

2. I am aware of no technical errors or omissions.

3. The report is clear and logical except for a minor issue. The first paragraph on p 108 is somewhat confusing. The text on line 5 (p108) indicates that half-life data need to be considered but does not indicate which half-life. Half-life in water? Half-life in the body? Also, this paragraph might benefit from a conclusions sentence. Agreed, the half-life data suggest that any change in lipids wouldn't be instantaneous. Is this expected to only be a minor problem or something more important? In general terms, when one challenges a fundamental assumption in a derivation it represents a major problem.

4. The conclusions drawn and recommendations provided are supported by the body of the text. It was somewhat curious that the recommendation section (p110-111) does not indicate the need to perform sensitivity analyses, yet two such analyses are mentioned in the preceding text.

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A final note is that the text of sections II and III should be proofread for typographical errors. I note below a few typos, but I am sure I didn't catch them all.

P90, line 20 "other studies that indicating..."

P92, line 17 "it is the Panel suggests.."

P97, line 35 "PFOS are of 20 ng/L.."

P99, line 15. The paragraph starts, "To summarize the Panel.." without ever indicating what is being summarized.

P115, line 12 Is it Appendix C that includes the CVD risk information and not Appendix A?

Comments from Dr. Amanda Rodewald

1) Were the charge questions to the Committee adequately addressed?

The responses include sufficient and impressive information to address the charge questions, yet I often felt that I needed to read between the lines and infer the "answer" to the question. The level of detail, organization, and phrasing sometimes made that difficult, despite a commendable job by the committee for their thorough evaluation.

For example, the General Comments in response to Charge Question 2A didn't seem to directly answer the request to comment on the strength of evidence for endpoints. The recommendation on page 15 also seemed to be a bit sideways because it emphasized the need to focus on the endpoints with the strongest evidence without providing an assessment.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No

3) Is the draft report clear and logical?

I found the organization of the report to be a bit confusing and difficult to follow, especially when there were multiple sub-sections and even multiple "Recommendations" sections for each individual charge question (e.g., ~12-page response to charge question 2.A with four different sections labeled "Recommendations"). Use of fewer subheadings (e.g., Background) might improve continuity and reduce some of the confusion.

Responses to charge questions sometimes were worded in ways that struck me as somewhat tangential. For example, the opening sentence of the recommendations on page 6 began with "Although it is not possible at this point to establish a protocol for the existing review

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process...”. However, the charge question did not seem to mention anything about establishing a protocol.

I would suggest including (preferably near/at the beginning) a simple declarative statement that answers the charge question using the same terminology and phrasing before providing details or other relevant information.

- 4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Emma Rosi

This committee report is thorough and provides excellent recommendations for improving the “Review of EPA’s Analyses 16 to Support EPA’s National Primary Drinking Water Rulemaking for PFAS”. I concur with the committee responses. I agree that consistent terminology and approaches are needed for this type of assessment. The recommendations outlined will improve the transparency and consistency of this process. In addition, I concur that limiting the use of older studies should be avoided or clear justification should be provided. The recommendation to include the list from the *Guidelines for Carcinogen Risk Assessment* in the document with relevant discussion and citations seems like a very useful addition. I also agree with committee’s suggestion that the “potential applicability of different approaches and their implications” for considering mixtures especially in the case of PFAS, as they can co-occur. Understanding the influence of mixtures is a frontier in toxicology, but it is necessary because of the complexity of the chemical mixtures that are now present in drinking water and surface waters in general.

Although I am not an expert in human health and drinking water assessments this draft review provides clear justification and recommendations for how EPA can improve this process and documentation.

Comments from Dr. Jonathan Samet

1. *Were the charge questions to the Committee adequately addressed?*

Yes, the committee carefully addressed the charge questions, providing in-depth responses. It covered the EPA’s methods and findings carefully, even reviewing critical studies and offering references.

2. *Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?*

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No, the report covers all critical issues raised by the four documents.

3. *Is the draft report clear and logical?*

Yes, the structure of the report appropriately follows the charge questions and comments and recommendations are appropriately placed.

4. *Are the conclusions drawn or recommendations provided supported by the body of the draft report?*

I recommend that consideration be given to an overarching recommendation on how the sweeping methodological concerns described in the report should be addressed. The comments make clear that EPA's approaches to gathering, synthesizing, integrating, and applying evidence are lacking and not the "state-of-practice. Unfortunately, serious flaws are documented with all aspects of the systematic review and evidence integration steps, including not having a protocol; uncertain approaches to assessing evidence quality; inadequate narratives for and weight-of-evidence determinations around causation. Systematic review approaches are now being applied to gathering mechanistic and toxicological data, but were apparently not utilized by EPA.

The report points to approaches that have been developed within the agency for systematic review and externally to EPA. Various programs within the agency have developed approaches for using systematic review: the IRIS Program, TSCA, and the ISA Program. Committees of the National Academies of Science, Engineering, and Medicine have provided a number of reports on the methods used by these programs that are applicable here. It appears that there is insufficient cross-talk across the agency, as similar concerns have been voiced over time about reviews in other programs. Steps have been taken to improve processes.

Given the well-documented problems with the reviews in the documents, does there need to be an over-arching recommendation that they need to be redone, following the state-of-practice for systematic review and evidence integration? A patchwork set of fixes will leave the documents open to questions about their findings and conclusions.

The letter to Administrator Regan includes the following paragraph:

The SAB recognizes the time constraints for completing the rule-making process and is supportive of the EPA's efforts to utilize the latest scientific findings to inform their decisions. The SAB applauds the agency's efforts to develop new approaches for assessing the risk of PFAS mixtures and the benefits arising from reducing exposure to these chemicals.

Should there be an additional sentence, such as: *However, the SAB considers these supporting documents to have methodological flaws that could undermine the rule-making process and*

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urges that these problems be addressed with revisions that represent the state-of-practice for gathering and using evidence for decision-making.

For me, this is the “bottom-line” from the report. The SAB should say this explicitly.

Comments from Dr. Peter Thorne

5. Were the charge questions to the Panel adequately addressed?

The charge questions were addressed with clarity and comprehensive descriptions of concerns.

6. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

None that I found. The report is very thorough. Despite using systematic review, the panel identified key publications and data that were missed. Inclusion of these studies will strengthen the draft MCLG document.

7. Is the draft report clear and logical?

The report is clearly written and the organization is logical. The panel and staff are to be commended for a great job.

Minor points:

The letter to Administrator Regan says “EPA should focus on those health outcomes that have been concluded to have the strongest evidence, including the liver, immune system, serum lipids, fetal growth, and cancer.” I note that “liver, immune system, serum lipids, fetal growth” are not health outcomes. Perhaps these should be listed as “... liver disease, immune system dysfunction, serum lipid aberration, impaired fetal growth, and cancer.” Also, in the Administrator letter “BMD” is not defined at its first use. “RSC” and “ASCVD” are not defined.

8. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

There were many specific and actionable recommendations. These were consistent with the concerns raised and were well supported by the text.

Comments from Dr. Godfrey Uzochukwu

Quality Review Questions for the SAB PFAS report

1. Were the charge questions to the Panel adequately addressed?

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- **Charge Question #1- Study Identification and Inclusion**

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.

Response: A diagram or flowchart depicting the overall process of study identification and inclusion will be helpful. This reviewer concurs with the Panel's overall comments, problem formulation and protocol development, recommendations, evidence evaluation, data extraction, evidence synthesis, recommendations and additional peer-reviewed studies that could inform hazard identification and toxicity value derivation.

- **Charge Question #2A - Noncancer Hazard Identification**

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?

Response: "...The 2016 HESD for PFOA concluded that there was substantial evidence for human effects of PFOA, as follows: "Human epidemiology data report associations between PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney)" and that "...human data identified significant relationships between serum levels and specific indicators of adverse health effects..." This reviewer concurs with the Panel recommendation that issues related to the strength of evidence for PFOA and PFOS exposure and increased serum cholesterol be discussed clearly and thoroughly. This reviewer does not feel comfortable with strong vs suggestive evidence. The panel noted that terms such as "suggestive evidence," "moderate evidence," and other seemingly interchangeable terms are used in sections on different health outcomes. These terms are not defined in the draft MCLG documents, and it is unclear whether there is an intended difference among these seemingly similar terms. This is a concern.

- **Charge Question #2B. Elevation of ALT**

Elevation of liver serum biomarkers in humans is frequently used an indication of liver injury, although it hasnot 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.

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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.

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.

- i. Are you aware of additional studies that support the ALT levels as markers of adverse liver effects? Please provide citations.*
- ii. Are there other adverse liver endpoints identified in the epidemiological literature that need to be considered?*

Response: SAB Panel does not 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 for the following reasons. This reviewer is not aware of any additional studies or other adverse live endpoints in the literature that need to be considered.

- **Charge Question # 3- Cancer Designation**

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.

Designation of PFOA as a “likely carcinogen”

Response: SAB Panel in general agrees that: a) the evidence for potential carcinogenicity of PFOA has been strengthened since the 2016 HESD; b) the results of human and animal studies of PFOA are consistent with the examples provided above and support a designation of “likely to be carcinogenic to humans”; and c) the data exceed the descriptors for the three designations lower than “likely to be carcinogenic”. The Panel cited California EPA (2021) conclusion that PFOA and PFOS should be evaluated as carcinogens for the setting of Public Health Goals (analogous to MCLGs) for PFOA and PFOS.

- **Charge Question #3 – Cancer Slope Quantification**

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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. Does SAB support the selection of this CSF in the derivation of a risk specific dose for PFOA (i.e., the concentration of PFOA in drinking water that would have a one-in-1-million chance of an increased cancer risk)? If not, please provide input on the strengths and weaknesses of the other candidate CSFs that EPA derived. [wording was revised (strikeout) before Panel deliberations].

Response: The Shearer et al., 2021 study is a prospective epidemiologic study that investigated the association between exposure to eight PFAS, including PFOA, and RCC risk, with PFAS measurements for all subjects in serum collected prior to RCC diagnosis. The SAB Panel noted that EPA selected the Shearer et al., 2021 study for CSF derivation. The systematic review conducted by EPA categorized the overall confidence in this study as “medium,” due to a *deficiency in controlling for confounding, and adequate confidence in selectivity and sensitivity* of the study (according to Figure 123, though not specifically described in the text). The Panel agreed with this classification, noting some merits and several limitations of the study design and overall significance of the results.

- **Charge Question #4 - Human Toxicokinetic 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).

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.

Response: The SAB Panel agreed that for adults and chronic exposure, the PFOA and PFOS compartmental models for adults (not pregnant or lactating females) are adequate for use in HED determinations. SAB Panel noted that there is also general agreement that the assumption of a constant half-life and volume of distribution for human adults is reasonable. Additionally, the assumptions of steady state are reasonable, given the long half-life of each molecule. ***The Panel notes that this approach is highly empirical and limited when looking to the future and using this model to ask questions about mixtures.***

- **Charge Question #4 - Animal Toxicokinetic Model**

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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.

Response: The SAB Panel agrees with the selection of the Wambaugh *et al.* 2013 model for the calculation of internal dose metrics. The rationale for the choice of the model is clearly described. If a decision is made to use RfDs based on animal studies in the final document, the animal model will become an important part of the basis for the MCLGs.

- **Charge Question #5A- Epidemiological Study RfD Derivation**

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?

Response: SAB Panel noted several different issues in considering the adequacy of the control for confounding. These issues include correlated exposure to other forms of PFAS, role of shared physiology in affecting biomarkers, and role of SES and potential for residual confounding.

- **Charge Question #5B- Epidemiological Study RfD Derivation**

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?

- If so, please explain your justification.*
- 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.*

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Response: Yes, the Panel agreed with the selection of the critical study, Grandjean *et al.* (2012), and the critical effect, suppression of a vaccine response in children exposed during development, as appropriate for the derivation of chronic RfDs for PFOA and PFOS. There are concerns. The critical effect is a reduction in antibodies produced in response to a vaccine in children exposed to higher levels of PFOA or PFOS compared to children with lower levels of exposure. Reduction in antibodies to a vaccine represents the failure of the immune system to respond to a specific challenge and is considered an adverse immunological outcome.

- **Charge Question #5C. Epidemiological Study RfD Derivation**

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.

Response: SAB Panel supports the use of 5% BMR for decrease in antibody response. However, stronger justification of the significance and relevance of the decreased antibody response in comparison with other adverse outcomes (e.g., decreased birth weight, elevated serum ALT, increased cholesterol) will strengthen the rationale.

- **Charge Question: #5D. Uncertainty Factors**

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.

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

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

Response: The SAB Panel noted that in section 4.1.5 of the PFOA (pp. 337 – 339) and PFOS (pp. 308 – 310) documents, EPA applied a value of 1 for interspecies (UFA), subchronic-to-chronic (UFS), LOAEL-to-NOAEL (UFL), and database (UFD) uncertainty factors. A UFA of 1 was selected because the RfDs were developed with human data. A UFS of 1 was selected because the critical effects (decreased antibody response to tetanus or diphtheria vaccine from exposure at age 5) were the result of a shorter-than-chronic exposure that is more sensitive than the chronic effects of PFOA and PFOS. A UFL of 1 was selected because the RfDs were based on a BMDL. Finally, a UFD of 1 was selected because the database includes numerous medium- and high-quality studies and a more sensitive endpoint than the critical effect is not expected. For both PFOA and PFOS, EPA applied a default value of 10 for the intraspecies (UFH) uncertainty factor to account for variability within human populations based on intrinsic and extrinsic factors that can influence response

- **Charge Question #6 - Relative Source Contribution**

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.

i. *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*

Response: No

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

Response: RSC of 20 percent (0.20) for PFOA and PFOS is adequately supported and clearly described. SAB Panel concluded that the recommended Relative Source Contribution (RSC) of 20% in the draft MCLG documents is appropriate for the PFOA and PFOS Reference Doses

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(RfD) development. A 20% RSC is the default value specified in the U.S. EPA (2000) guidance for deriving ambient water quality criteria for the protection of human health, which is cited as the basis for the RSC selection in the draft MCLG documents.

SECTION II- MIXTURES APPROACHES

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

- **Charge Question #1- Dose Additivity Assumption**

*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 (dose additivity based on common endpoint of toxicity or health effect) for a component-based mixture valuation of PFAS under an assumption of dose additivity.

Response: The SAB Panel was in agreement with use of a similar toxicity endpoint/health effect instead of a common MOA as a default approach for evaluating mixtures of PFAS. This approach makes sense because multiple physiological systems and multiple MOAs can contribute to a common health outcome. Human function is based on an integrated system of systems and not on single molecular changes as the sole drivers of any health outcome. The Panel concluded that rather than the common MOA, as presented in the EPA draft mixtures document, common physiological outcomes should be the defining position. Consider a health outcome such as elevated blood pressure (not one for PFAS or PFOS but just a general example). It is known that there are many different physiological systems that contribute to regulation of blood pressure beyond the renin-angiotensin system (Joyner and Limberg, 2014). The Panel notes that the assumption of dose additivity for chemicals that cause a common toxicological effect through different MOAs is supported by results of a recent study of effects of mixtures of compounds with different MOAs on craniofacial malformations in zebrafish (Van Der Ven *et al.*, 2022) and an accompanying commentary (Kortenkamp, 2022).

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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).

- Charge Question #2- Hazard Index Approach

*Section 4.3 (**Hazard Index, HI**) of the framework 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.

Response: The SAB Panel noted that screening level Hazard Index (HI) approach, in which Reference Values (RfVs) for the mixture components are used regardless of the effect on which the RfVs are based, **is appropriate for initial screening** of whether exposure to a mixture of PFAS poses a potential risk that should be further evaluated. There are several challenges and considerations relevant for PFAS mixture risk assessment. These challenges include lack of toxicology data, use of TOSHI approach, consideration of probabilistic methods for HI/TOSHI calculations to estimate risk, challenges with implementation and limitations.

- **Charge Question # 3- Relative Potency Factor**

*Section 4.4 (**Relative Potency Factor, RPF**) of the framework 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 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.

Response: SAB Panel agreed that the RPF approach is a reasonable methodology for estimating risk associated with mixtures of PFAS. An alternative methodology was not suggested. The Panel noted that the RPF approach is a more data intensive approach, as compared to the Hazard Index methods, which is likely to see a greater application for PFAS. They expressed concern

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that there are many PFAS with little or no data and an approach is needed to address mixtures where comprehensive datasets do not exist. The Panel agreed that the EPA should reconsider the tiered approach that is presented in Figure 4-1 of the draft mixtures document. They also noted that New Approach Methods (NAMs) may be useful in filling data gaps for some PFAS given the large number of these substances that lack data.

B. Please provide specific feedback on whether the proposed RPF methodology in the framework is scientifically supported for PFAS mixture risk assessment.

Response: SAB Panel concluded that the framework needs further elaboration and clarification before it can be implemented.

• Charge Question #4- Mixture BMD

Section 4.5 (Mixture BMD) of the framework 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.

Response: The SAB Panel agreed that the Mixture BMD approach is a reasonable methodology for estimating a mixture-based POD with caveats.

B. Please provide specific feedback on whether the proposed Mixture BMD methodology in the framework is scientifically supported for PFAS mixture riskassessment

Response: The SAB Panel concurred that the approach is scientifically supported for PFAS mixture risk assessment, and that both its criteria for application and its potential limitations are well described. Throughout the draft framework for PFAS, the EPA clearly explained the BMD process and approach and appear to have followed the basic recommendations in the EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (2000).

SECTION III- BENEFITS FROM CVD REDUCTION

EPA's draft Analysis of Cardiovascular Disease (CVD) Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water

Overall Charge Question

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EPA is seeking SAB evaluate 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.

Response: The Panel recommends more discussion as to the rationale for selecting this endpoint for risk reduction analysis (e.g., strengthening of the hazard conclusion with respect to PFOA or PFOS, availability of dose-response data from which to derive a dose-response function or risk-specific dose estimates, strengthening of data connecting changes in biomarker to changes in morbidity or mortality, and availability of data for monetizing benefits).

The SAB Panel expressed concern about the apparent discrepancy between this document's focus on CVD risk, and the draft MCLG documents' conclusions that the evidence of CVD was not sufficient to form the basis of a RfD.

- **Charge Question #1- EPA's Meta-Analysis**

Section 4.2 presents EPA's meta-analysis for the total cholesterol dose-response function.

- 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.*

Response: SAB Panel noted that the approach to identifying and managing the literature on PFAS and cholesterol is reasonable for this purpose, with little basis for more esoteric or complex approaches and suggested the use of other approaches to set the stage for a sensitivity analysis. The meta-analysis study selection criteria were well reasoned, and EPA identified 14 relevant studies for analysis.

- 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.*

Response: The SAB panel noted that in the slope estimation, the associations for HDLC and PFOA and PFOS were positive, albeit not statistically significant, which may not warrant exclusion of HDLC from consideration in the CVD risk reduction analysis. Selecting endpoints solely on the basis of having statistically significant positive effects may exclude meaningful associations that are imprecise. The SAB Panel concluded that further explanation of the basis for excluding this indicator from detailed consideration would be helpful. In addition, the Panel

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concluded that the approach for estimating the dose-response function using the Atherosclerotic Cardiovascular Disease (ASCVD) risk assessment tool is likely a reasonable choice. It was developed by leading cardiovascular disease researchers, it is widely used despite some limitations, and there is no reason to invent a new tool for the purposes of this exercise. In fact, it seems the instrument was developed for exactly this purpose, to estimate the impact of interventions including modifying cholesterol levels, and the reduction of PFAS in drinking water is one of the ways this might be accomplished. SAB Panel noted that NHANES has been repeatedly analyzed for the association between PFAS and total cholesterol levels, using meta-analysis may not yield additional value compared with the approach Dong *et al.* used in the 2019 publication. If the results were from different study populations, meta-analysis results would provide a useful method to aggregate across these populations. The Panel agreed that the approach for estimating the dose-response function using the Atherosclerotic Cardiovascular Disease (ASCVD) risk assessment tool is likely a reasonable choice.

- **Charge Question #2- EPA's Life Table Approach**

Section 5.1 presents EPA's life table approach methodology.

i. 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.

Response: The SAB panel concluded that the application of the life table methodology to evaluate CVD risk reduction from treatment of PFOS/PFOA is reasonable, and the methodology is generally well-described. The advantage of the life table approach is that it takes into

consideration the timing of the treatment and the aging of the population, which captures the impact of treatment on partially treated populations (i.e., those born before treatment occurred). The proposed methodology, however, involves many assumptions and modeling decisions that may affect the estimates of the mortality/morbidity impacts, such as excluding individuals with pre-existing conditions and tracking post-acute CVD mortality for up to five-years after a CVD incident. These modeling assumptions are likely to omit components of CVD benefits. Reorganization of the Table is suggested.

ii 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.

Response: The SAB Panel noted that the ASCVD model predicts the probability of a first CVD event in the following 10 years. EPA estimates the annual risk as the constant yielding the same 10-year risk (i.e., $(1 - x)^{10} = (1 - y)$ where x is the annual risk and y is the 10-year risk). This approach seems adequate.

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iii 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.

Response: The ASCVD model is calibrated to data from epidemiological studies that establish a relationship between total cholesterol and CVD risk but SAB panel noted that such studies do not by themselves provide evidence that a change in total cholesterol will change CVD risk, nor do they provide information about whether the effect of a change in total cholesterol on CVD risk depends on the source of the change. The Panel recommends that EPA provide further discussion of the accuracy of the model predictions in sub-groups with varying levels of social deprivation. The Panel recommends that EPA evaluate whether inclusion of HDLC would influence the results of the modeling. SAB Panel recommends that EPA evaluate whether inclusion of HDLC would influence the results of the modeling.

- **Charge Question #4- Limitations and Uncertainties**

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?

Response: The SAB Panel concurred that EPA was generally clear in describing the **individual** contribution of sources of uncertainty in Section 7 and Appendix E of the Analysis of CVD Risk Reduction document, and the approach to characterizing some uncertainties using Monte Carlo analysis in Appendix E of the EPA draft CVD document. Additional specific areas needing further clarification are listed in Appendix A of this report.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Minor typographical errors

3. Is the draft report clear and logical?

**Yes, except assumptions and suggested ideas.
Report should be data driven.**

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

**Yes
Well written report**

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A compilation of your quality review comments on the CCL5 and PFAS reports will be posted with the meeting materials on the SAB website at the following URL.

https://sab.epa.gov/ords/sab/f?p=114:19:14377151500644:::RP,19:P19_ID:975