

**Comments from Members of the Chartered SAB on the SAB Draft Report:  
Science Advisory Board Review of the IRIS Draft Toxicological Review of  
Trimethylbenzenes (5/1/2015)**

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## Comments from Lead Reviewers

### Comments from Dr. George Daston

We were asked to address four specific questions as part of the quality review.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;
2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. whether the Committee's report is clear and logical; and
4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

General Comment: I was a lead reviewer on this draft report and the draft report on the IRIS assessment for ammonia. Both reports had the same four general charge questions, requesting feedback on how well the new IRIS format has complied with the NRC recommendations stemming from its 2011 formaldehyde review. Given that the charge questions are the same, the SAB should consider combining the responses from both reports into one set of consistent recommendations.

Question 1: I believe that the charge questions were adequately addressed. The review is thorough and provides a number of constructive recommendations for each charge question. As noted in my general comments, the SAB should consider combining the responses to the general charge questions with those from the ammonia draft report to ensure consistency.

Question 2: I found the report to be comprehensive. There were a few points that could be clarified. First, the report mentions in several places that EPA should have the PBPK approach used to establish a RfC and RfD peer-reviewed independently. Why? The roster for the subcommittee preparing the draft report contains the names of several experts in pharmacokinetics. The section of the report critiquing the model appears to be thorough, with constructive suggestions. What more would be gained by having another peer review?

Second, there appears to be inconsistent advice on the use of a structure-activity approach using related compounds to fill data gaps. Some of the advice seems to be encouraging, while elsewhere the report suggests that this would just be replacing one uncertainty (about database completeness) with another (extrapolation across chemicals). The report should provide clearer guidance as to which analogs should be selected (and why), and the extent to which they can be used (e.g., to fill a data gap, to support a weight-of-evidence argument of a class-level effect on specific endpoints, etc.). Also, it was not clear to me why this approach was suggested for some, but not all, endpoints. Especially, the report concurs that there was inadequate evidence of carcinogenicity, despite the fact that there are carc studies on some of the analogs suggested for read-across for non-cancer endpoints.

Question 3: The report was logical and the recommendations are clear and comprehensive. The one area that needs tightening is in providing guidance on the use of analogous compounds to support the assessment. As noted in my response to question 2, the report does not provide enough guidance on criteria for analog selection, or on how the analogs should be used (qualitatively or quantitatively). It is not clear why this was suggested for non-cancer endpoints but not to cover data gaps for cancer.

Question 4: The conclusions and recommendations are supported by the body of the report.

### **Comments from Dr. Nancy K. Kim**

#### General Comment

The report is well done, responds to the charge questions, and is well written. In a few places some clarification or rewriting would help. For some of the charge questions, a list of major comments is give at the end of the response. A listing is not needed for all the questions, but adding such a list for a few of the longer or more complicated responses would be helpful (see comment h under question 3).

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

Yes.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
  - a. Not that I noticed, but suggestions are made in under question 3 to help clarify some points that were unclear to me.
  - b. Appendix B is the panel's review of EPA's PBPK model internal metrics. The panel also recommends that EPA conduct an independent peer review of the PBPK model and modeling results if it is a new version, previously unpublished or is a modification of a published model. In this case, does the panel want EPA to modify the PBPK model based on the panel's review, followed by EPA having a independent peer review? Providing EPA with specific recommendations on how to proceed may be helpful.

3. Is the draft report clear and logical?

Letter to the Administrator

- a. Page 1, line 33. "Response to the implemented to address" should probably be something like "Response implemented to address."
- b. Page 1, line 37. Suggest editing this line to something like "several assessments nearly developed. For these documents, the agency is focusing on.... Consider eliminating the words better and considered.
- c. Page 2, lines 8 – 24. Consider adding a sentence that the SAB panel did a peer review of the PBPK model and included it in Appendix B of its report. The same sentence could be added to the Executive Summary,
- d. Page 2, paragraph beginning on line 26. This paragraph highlights using 1,3,5-TMB data to develop candidate toxicity values for developmental and liver

toxicity. On page 35 of the report, the panel suggests that these candidate toxicity values be considered for 1,2,3- and 1,2,4-TMB as well. Consider including this concept in this paragraph.

## Report

- a. Page 5, paragraph beginning on line 33. This paragraph, especially the beginning could be clearer. The second sentence isn't a sentence and the three sentences describing the issues are statements don't specify the issue, leaving the reader to make inferences. For example, the first issue (assuming I have the correct interpretation) could be rewritten to say "The SAB identified additional potential uses of the candidate toxicity values developed to select the overall toxicity value and the TMB document should include those uses." The second issue could be that the document needs to include exposure to vulnerable life stages and the third issue might be that the applying uncertainty factors to go from subchronic RfCs and RfdDs to chronic values is not valid.
- b. Page 6, line 21. The panel should consider whether the SAB wants to recommend that Section 1 include an overarching statement about what IRIS seeks to accomplish, etc.
- c. Page 8, line 1. Clarify if this sentence is to state that organ-specific reference values should not be included in the document.
- d. Page 11, line 16. Can the phrase "with all the endpoints clustered study" be clarified?
- e. Page 11, line 21. Does the panel want to make the final statement in this paragraph a recommendation?
- f. Page 11, line 29. Can the sentence beginning "It is perhaps unfortunate" be clarified?
- g. Page 21, line 23. What exposure level is the sentence "Agreement was better at the lower exposure level" referring to? Could additional information be added because the paragraph implies that the model is a better predictor at higher exposure levels and that seems contradicted in the last part of the paragraph. How should the last sentence in the paragraph be viewed in light of the consistently underpredicted blood levels mentioned in the second half of the paragraph. If this sentence is saying that although the levels are underpredicted, the differences are minor and not important. Also, without more detail, it isn't clear if the words post-exposure levels are different than the levels discussed in the 3 previous sentence.
- h. Page 23, line 20. The panel provides many comments/suggestions in answering this charge question. Adding a bulleted list of the more important comments at the end of this discussion would help to highlight the critical points.
- i. Page 24 through 26. Two charge questions are addressed in these pages. Issues are raised about the reversibility of effects, the RfC calculations and cumulative toxicity and rotarod failures (among others) in answering one charge question. In answering the second charge question, decreased pain sensitivity is the critical effect in calculating the RfC. If the reader hasn't read the TMB document, it isn't clear how the two responses relate. Could a brief couple of sentences be added to help clarify the relation between the responses to these two charge questions?
- j. Page 29, line 11. Response to charge question. Add some language in the beginning of the response to make it clear if the Korsak and Rydzynsi, 1996 study used to derive the RfC for 1,2,3-TMB is the previously discussed 1,2,4-TMB study or a 1,2,3-TMB study (See wording of charge question). If readers haven't read the IRIS document,

the wording introduces uncertainty.

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

Yes, although some suggestions are made in answering question 3 that would help clarify some comments.

#### Minor comments

##### Letter to the Administrator

Page 2, line 22. Insert comma after 1,2,3-TMB.

##### Report

1. Page 1, line 32. Remove repeat of previous sentence.
2. Page 2, line 39. Remove second period after TMBs.
3. Page 3, line 16. Form should be from.
4. Page 7, line 39. The “are” between Preamble and appear should be removed.
5. Page 9, paragraph beginning line 3. Consider editing to improve clarity.
6. Page 9, line 38. Should “studies” be “studies””? Should the “as” in the phrase are as consistent be removed?
7. Page 12, line 35. Insert the word “should” between sections and have.
8. Page 13, line 36. Remove the comma between options and is since it separates the subject from the verb in the sentence.
9. Page 14, line 36. Typo – two periods at end of sentence.
10. Page 19, line 24. Remove “of” between review and these.
11. Page 22, line 36. Period is needed after revisiting.
12. Page 31, line 33. Insert comma after unsuccessful.
13. Page 36, line 26. Insert space between TMB and or.

#### **Comments from Dr. Lois Lehman-McKeeman**

The charge questions have been adequately addressed. The report is extensive in its review, and generally well-organized. There do not appear to be any technical omissions, but as noted below, issues of mixed opinions do not seem to be addressed directly, leading to a sometimes circuitous logic that is somewhat difficult to follow.

The SAB review provided an extensive response to enhancing the IRIS assessment documents. The comments are quite thorough and if incorporated, would definitely enhance the clarity and ease of reading these assessment.

The review panel was divided in its consideration as to whether toxicological data from C-9 mixtures (TMB isomers and ethyltoluene isomers should be considered in this assessment. In the panel’s review (page 14; section 3.1.4, starting line 24), the lack of a consensus was indicated. In the Executive Summary (page 2, lines 37-40), the panel indicates that studies on closely related deserves further discussion in the Assessment. However, when the consideration of C-9 is presented in Section 3.2.3, and there is no indication that there was a mixed opinion on whether these data are useful. As one example, Lines 29, page 19 states that the use of C-9 mixtures has “interpretive issues.” There is little clear indication of what such interpretative issues would be. Furthermore, although possible shortcomings are sometimes noted, the draft lacks clarity on providing perspective on what criteria should be used to consider C-9 mixtures or not. This section seems to somewhat lengthy, and in the end, inconclusive, so it is not really

helpful to EPA scientists. The section needs to be clarified with final recommendations to use the C-9 mixtures, if that was the final decision from the panel, and there needs to be clearer and more succinct indication of the potential strengths and weaknesses of considering these data.

The review provided on the PBPK modeling is quite helpful, with clear recommendations provided on how to improve the modeling as well as considering an option for benchmark dose modeling.

## **Comments from other SAB Members**

### **Comments from Dr. Joseph Arvai**

#### **1. Were the charge questions adequately addressed?**

Yes.

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

Not to my knowledge.

#### **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. Sylvie M. Brouder**

Q1) Charge questions adequately addressed?

Noting that I am not an expert in toxicology but am familiar with systematic review protocols and their use in a variety of disciplines, it appears that the charge questions regarding validity/justification in interpreting the science were thoroughly and comprehensively addressed. Regarding charge questions specific to the new methodology (Systematic Reviews (SRs)) being phased in as a common protocol for IRIS, some of the responses to charge questions on improvements could be strengthened with further clarification. For example, there is mention in the Executive Summary and in the main body of the report in response to charge questions on the adequacy of the search strategy of the need to expand the literature search to “other closely related aromatic solvents... to fill gaps in the TMB database.” This appears to blend and perhaps confuse two critical aspects of Systematic Reviews – the question formulation versus the

comprehensiveness/suitability and accurate portrayal of the literature search strategy. The question of broadening the search strategy seems to be primarily about question formulation (noting that question formulation may require a preliminary search to refine the question). The charge question as posed seems more about the search strategy. To advance the rate of implementation of SRs in the IRIS methodology, it seems beneficial to distinguish/clarify these two distinct aspects in both responses to charge questions and in recommendations.

Q2) Technical errors or omissions / issues not adequately addressed?

A few miscellaneous points are as follows:

- On page 2/line 9 -11 of the cover letter to Administrator McCarthy, why is the SAB recommending that EPA provide a transparent and detailed discussion of selection rationale for the PBPK modeling approach when selection of the approach itself is being evaluated. Surely we are suggesting that, prior to any implementation, that the approach be justified in any documents detailing the intent/plan to implement an approach...??
- Note, there appears to be a sentence fragment in the Executive Summary (Pg. 2, line 26: “In addition, ...”) and confusion on singular versus plural (Page 2, line 28 – 29) on “concentrations” and “doses”
- Extra “.” On pg 2, Line 39 of Executive Summary
- Page 7/Line 39 “... appear are...”??
- Page 11/line 16: something missing in the phrase “with all the endpoints clustered study.”?
- Page 11/line 29-31: something seems not quite right with this statement.
- Page 22/line 36: missing “.”
- Page 31/line 4-5: a word missing in this sentence?

Q3) Draft report clear and logical?

Yes. Occasional statements lack clarity. For example, on page 7/line 4 – 6, it is not entirely clear what is meant by this one sentence paragraph suggesting that the over summarizing of existing guidance in Preamble might be interpreted as contradicting existing policy. This sounds like a major problem/criticism but it is hard to assess the statement’s relevance as it is given in a one sentence paragraph. Also, on page 8/lines 12 – 21, the first and third bullet points seem to address the same point... is clarification needed here?

Q4) Conclusions drawn / recommendations provided supported by body of draft report?

Yes. Note, in the Executive summary (and occasionally elsewhere), recommendations are not clearly stated or restated at the end of a paragraph where a reader often looks for reiteration or refinement that is present in the beginning of a paragraph which is subsequently followed by some nuanced discussion. For example, on page 3/Line 23-25 of the Executive Summary, the suggestion “to expand the description and importance... for sensitive life stages...” seems quite vague. Is this an opportunity to more clearly state the knowledge gap and give a more specific/actionable recommendation? Again, in the main body of the report, the paragraph on the process of systematic reviews (pg. 13/Line 22 – 31) offers some cautions but seems to end quite abruptly without offering a recommendation when the closing of the paragraph offers the natural opportunity to insert one. Is there something specific that the SAB can offer up to help in the successful implementation of SRs in the IRIS process? A final example of somewhat ambiguous close to a paragraph when a recommendation or a refinement on recommendation could be

offered is on Page 28 with the discussion on UFs. The report notes agreement with the EPA's proposal of for using a value of 3 but then proceeds with a fairly long description of the SAB's discussion on the use of the value and on differing opinions. The end of the discussion seems a natural and important opportunity to capture how/why the SAB eventually reached consensus on the recommendation offered in the first sentence of the section. In its current presentation, the text suggests that the SAB was somewhat at odds with what was recommended. If this is not the case, this needs to be clarified.

Regarding the specific recommendation to provide citations for all 4300 citations and group them according to exclusion rationale ~ This recommendation seems to direct effort more toward the perhaps onerous listing of all papers initially included in a first round of search versus emphasizing the need for comprehensively characterizing inclusion/exclusion criteria. Given that the protocol itself is also being developed, is it as or even more important to emphasize in the recommendation the development of a process for developing/refining inclusion/exclusion criteria that could be applied to a search that nets 10- or 100-fold the number of citations? In other words, can the recommendation be broadened to encompass future IRIS reviews where it would be in-efficient or prohibitive to list/categorize all articles returned with a given search strategy?

Minor points:

Pg. 17/Line 36 – 38: This recommendation seems relevant only to qualitative SRs. In a quantitative SR with appropriate use of statistical meta-analysis, studies with non-significant trends can be appropriately combined with studies with significant effects. Does this statement require further clarification?

### **Comments from Dr. Costel Denson**

This report is extremely well written. It is clear, concise and presents the information in a well-organized fashion.

1. Were the charge questions adequately addressed?

Yes

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

None

3. Is the draft report clear and logical?

Unequivocally, the report is clear and logical.

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

Yes.

### **Comments from Dr. Michael Dourson**

Purpose: to describe the role and involvement of chartered SAB members and Board liaisons in the quality review of draft advisory reports developed by SAB panels, subcommittees, and work groups.

1. Were the charge questions adequately addressed?

Yes, the committee was well balanced and appeared to discharge their responsibilities with aplomb.

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

I was under the impression, perhaps incorrect, that EPA's Office of Pesticides Programs also has risk assessment values for these chemicals. If so, what are they? And a natural follow-up question would be whether our NCEA colleagues worked with their OPP counterparts to develop one EPA position? Having more than one current EPA risk assessment value is counter to the spirit, if not the letter, of EPA's Integrated Risk Information System (IRIS). Recent findings on a large number of pesticide values on IRIS that do not match current OPP values is problematic (<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2014-0211-0019>), but I understand that EPA is working to resolve this.

3. Is the draft report clear and logical?

Yes, the report was very easy to read and it made sense.

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

Yes, the conclusions seemed very reasonable and the several recommendations were supported. In particular,

Page 3, line 14. The consideration of the UFD in the development of candidate toxicity values for multiple endpoints.

The SAB committee is absolutely correct in that the development of target organ specific RfDs, as previously recommended by Moiz Mumtaz and his colleagues in the 1990s<sup>1</sup>, WILL change the UFD considerations. One needs to determine the theoretical grounds for developing the UFD for such target organ toxicity values, similar to what EPA did for the UFD in the first place<sup>2</sup>.

Page 3, line 27. Development of subchronic risk assessment values.

The SAB committee is also correct here; developing subchronic RfDs/RfCs, similar to EPA's Office of Water and Pesticide Programs, is important. In fact, removing the subchronic to chronic UF from the lifetime RfD or RfC should approximate the subchronic RfD or RfC, and is the common practice when a lifetime RfD or RfC is available and a subchronic value is needed in the field.

Page 7, line 4. Preamble consistent with existing guidelines.

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<sup>1</sup> MUMTAZ\*, M.M., POIRIER, K.A. and R.C. HERTZBERG. Feasibility of Developing Target-Organ Toxicity Doses (TTDs) for Estimation of Toxicity of Chemical Mixtures. Annual meeting of the Society of Toxicology, New Orleans, LA, March 1993.

<sup>2</sup> Dourson, M.L., L.A. Knauf, and J.C. Swartout. 1992. On Reference Dose (RfD) and Its Underlying Toxicity Data Base. *Toxicology and Industrial Health*. 8(3): 171-189.

This SAB committee makes a good recommendation here that is similar to the recommendation made by the SAB committee on ammonia.

Page 12, line 3. Upfront summaries of toxicity.

I very much like the committee's suggestion here for it allows an explanation of what types of toxicity a particular chemical might evoke, and since all chemicals cause toxicity, might more easily allow a distinction among potential chemical hazards.

Page 28, line 37. Discussion of the database uncertainty factor.

The discussion seems appropriate. One question, however. Were the subchronic studies all of the same species? If so, and if the 2-generation study is missing along with developmental toxicity studies, then this argues for a 10-fold UFD. Please clarify.

### **Comments from Dr. Robert J. Johnston**

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

Yes, the report has adequately addressed the charge questions.

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

There are no technical errors or omissions that are not adequately addressed by the draft report.

One issue that warrants additional emphasis in the SAB report is the potential consequence of the lack of clear and formal systematic review protocols. The SAB review notes that (p. 10) "the primary literature search should be comprehensive and subjected to an orderly process of systematic review." It notes that processes for such systematic reviews are in progress and still need development. It further areas in which the literature search strategy requires additional information (e.g., exclusion criteria and implementation of those criteria). However, the SAB review does not discuss the risk of selection biases that can affect results of data syntheses and meta-analyses (or literature reviews more broadly) that are not subject to such rigorous systematic review processes. This concern does not appear to be recognized sufficiently in the *Science Advisory Board Review of the IRIS Draft Toxicological Review of Trimethylbenzenes* or the SAB review of this report. While I agree with the SAB review that the Agency is to be commended for its progress thus far, I believe that more emphasis should be given to the need for systematic review protocols.

3) Is the draft report clear and logical?

Yes, the draft report is clear and logical

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

Yes. However, as noted above, there should be additional emphasis on the need to move towards the application true systematic review protocols.

#### **Comments from Dr. Elizabeth Matsui**

1. Were the charge questions adequately addressed?

YES

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

For toxicology- and risk assessment-related content, I will defer to the reviewers with toxicology and risk assessment expertise

3. Is the draft report clear and logical?

Yes, overall, the draft report is very clear and logical.

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

YES

#### **Comments from Dr. James R. Mihelcic**

1. Were the charge questions adequately addressed?

Yes

2. Are there any technical errors or omissions in the report 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

Other issues

line 7 of page 17 (page 29 of the pdf), should the word “reference” be plural.

One line 11 of page 26 (page 38 of the pdf) should Gralewicz and colleagues be written as Gralewicz et al.?

Line 10 of Page 28 (page 40 of pdf) should “a UFs of 10” be written as “a UF of 10” ?

When concentration is written as ppm and then provided as mg/m<sup>3</sup> in ( ) (like on line 31 (page 43 of pdf), should temperature be provided, or this be made clear somewhere in document?

Line 1 of page 36 (page 48 of pdf), is the study referred to as Koch et al. really the study referred to as Koch Industries on previous page? (line 20 of page 35).

#### **Comments from Dr. James Opaluch**

- 1) Were the charge questions to the committee adequately addressed?

Yes

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

Not that I am aware of.

3) Is the draft report clear and logical?

There appears to be an inconsistency on page 6 of the report. On page 6, lines 15-16, the report indicates “The Preamble certainly should be no longer; as it stands, it is near the limit of what can serve as an overview and explanation.” But on lines 22-23, the report says “... but the SAB notes that it lacks any overarching statement about what IRIS seeks to accomplish, its ultimate purposes, and what its assessments are meant to represent to their users” This is important, but it difficult to see how to do this without making the Preamble longer. Lines 35-36 say “The SAB recommends that it include some discussion ... about the issues needing to be addressed, the prospects for addressing them with available data, and the uncertainties and plausible alternative interpretations that would need to be worked through.” The report should be explicit on resolving these apparent inconsistencies. For example, it might say “Below we suggest some additional details that are important to include in the Preamble, but we also suggest some other elements that might be eliminated or shortened, with a reference to the Guidance Documents for more detail.” I’d also recommend the report be careful about saying “The Preamble certainly should be no longer...” If the Report recommends additions and deletions, it might be appropriate for the Preamble to be somewhat longer. A recommendation like the Preamble should not be “significantly” (or “much”) longer might be more appropriate.

There is an editorial problem on page 7 line 39. “Some precepts in the Preamble are appear to the SAB as not consistent...”

Most sections end with an explicit summary of the recommendations relevant to the charge question. But the end of Sections 3.1.3, and Sections starting at 3.2.4, 3.2.5 do not include an explicit summary of recommendations. I think the explicit statement of summaries is good, and the sections should be consistent. Someone should also make sure that the all recommendations in the text match with the summaries.

Is there a reason that the discussion of the Charge Question on page 25, starting on line 37, and the Charge Question on page 29 starting at line 37 are not in stand-alone numbered Sections, like the others are?

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

Yes

### **Comments from Dr. Amanda D. Rodewald**

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

Yes. The draft report was thorough and provided useful feedback to the Agency.

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

No, not that I could find. However, I recognize the topic is outside of my area of expertise.

3) Is the draft report clear and logical?

Yes.

Page 10, Lines 31-33: This sentence is unclear to me and could be better clarified.

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

Yes.

On page 35, lines 41-42, the SAB panel stated that there was stronger scientific support for use of PBPK-extrapolated RfD for 1,2,4 TMB based on a neurotoxic endpoint. It would be useful if they provided references for this support.

#### **Comments from Dr. Daniel O. Stram**

1. Were the charge questions adequately addressed?

The SAB report covers both primary areas of the charge questions, i.e. implementation of the 2011 NRC review recommendations for the ISIS, and the scientific and technical analyses used to develop reference concentrations and doses for the TMB isomers.

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

None that I could detect

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 each recommendation is carefully supported in the report.

#### **Comments from Dr. Charles Werth**

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

Yes, they 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 find any technical errors or omissions.

3) Is the draft report clear and logical?

In most places the report was clear and logical.

However, I found some text in the letter to the administrator unclear because jargon was used or explanations appeared incomplete. Below are examples:

i) 2nd Page of letter, line 16: Is the recommendation for an independent review of the PBPK model in addition to the SAB review?

ii) 2nd page of letter, line 28: What is the "critical effect"?

iii) 2nd page of letter, lines 29-32: What endpoints and what studies are being referred to? Where do neurotoxicological effects come in? Were they used for inhalation values? Is this extrapolation from 1,2,4-TMB to 1,3,5-TMB?

iv) 3rd page of letter, line 1: Given the lack of data, is it reasonable for the EPA to expand on the importance of these analyses without further studies. Perhaps commenting on the potential importance of these analysis and the need for further data would be more appropriate.

Other suggestions to improve clarity in the report are:

v) Page 3, line 14: Not sure if UF\_D was defined earlier. If not, define here.

vi) Page 3, line 35: Since the development of subchronic doses is being proposed here, perhaps the aforementioned doses should be identified as chronic.

vii) Page 7: It's interesting that more than one report comments on the Preamble and different, sometimes contradictory suggestions are given. Should the SAB speak with one voice on the Preamble in the different reports?

viii) Page 7, line 27: Readers will use it as guidance so it seems it should be written as summary guidance with specific details referred to in reference documents/links.

ix) Page 7, line 39: Delete "are" before "Preamble".

x) Page 12, line 26: Delete "properties".

xi) Page 14, line 17: Is "gavage" a word?

xii) Page 16, line 44: Providing citations for 4300 papers when many of them may be easily discounted does not seem like a good use of space. I would lean towards providing the search databases and terms for the 4300 papers, how the search was narrowed to prune these down, and then what papers had to be systematically looked at to decide whether to keep. If the paper was looked at then a citation seems reasonable.

xiii) In various places I find the report too wordy. There seems to be too much reviewing of results before charges are addressed. For example, the last three paragraphs on page 21 and the first paragraph on page 22 largely recount the results of different studies without addressing the charge.

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

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

**Comments from Dr. Dawn J. Wright**

1. Were the charge questions adequately addressed? Yes, very much so, as far as I could tell.
2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report? Not that I am aware.
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