

**Preliminary Comments from Members of the Chartered SAB on the SAB report,
Review of EPA’s Draft Assessment entitled “Toxicological Review of Trichloroethylene”
 (October 2009)**

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Comments from lead reviewers

Comments from Dr. Thomas Burke

General observations

The toxicological review of trichloroethylene document represents one of the most comprehensive iris assessments ever conducted by the EPA. As a result of the NAS review and recommendations, and the advancement of EPA guidelines and methodologies, the assessment includes many components not included in past IRIS documents. The assessment includes

- A benchmark dose approach
- Improved presentation of PBPK modeling
- Detailed meta analysis of the epidemiological studies
- Examination of cancer and non-cancer endpoints
- Inclusion of multiple critical values for derivation of RfD and RfC
- Consideration of susceptibility and coo-exposures, including age-dependent adjustment factors

The review committee did an excellent job in presenting the major challenges with many of these evolving methods. The Report is exceptionally well written and organized. The committee addressed each question in a thorough way. The inclusion of recommendations at the end of each major question is particularly helpful and should be a model for SAB Quality Reviews.

One of the potential pitfalls in reviewing IRIS documents is the fact that there are many uncertainties and limitations in the data. In addition, the state of the science is constantly advancing. Therefore it is challenging to make recommendations to improve the assessment, while avoiding a potentially endless cycle of review and rewriting. The recommendations of the SAB report are very responsive to the questions, and also appear to be very practical. The recommendations will help to clarify the report and improve the presentation of the scientific basis for its methods, finding, and conclusions.

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Each of the original charge questions was very well addressed. The responses to the questions include the strengths and limitations, as well as a clear statement regarding support of the EPA method or conclusions. With the committee felt additional clarification is necessary practical recommendations are presented.

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

dealt with in the Committee's report?

There do not appear to be any technical errors or omissions in the report. The committee addresses each section of the charge questions very thoroughly.

3. Is the Committee's report is clear and logical?

The committee's report is written very clearly. It presents a logical approach to each of the charge questions including a discussion of each major issue. Limitations and concerns about the methods used in the document are clearly presented, along with practical recommendations to clarify and strengthen the document.

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

The conclusions and recommendations for each question are well supported in the text of the report. Where appropriate, specific methodological suggestions are presented, and appropriate references are included.

Comments from Dr. George Daston

1. Were the original charge questions adequately addressed?

I believe that the charge questions have been adequately addressed. The draft assessment of TCE is a complicated document. The literature on the toxicity of TCE is voluminous, and the assessment procedures used in the report were complicated and varied, including everything from PBPK modeling to meta-analysis of epidemiology studies. Therefore, the charge to the Committee was extensive. The Committee did a commendable job of addressing the charge questions. The advice provided to EPA is constructive and will make the final report scientifically stronger and more transparent.

I did find the Research Needs section of the Committee's report to be on the lengthy side. While I found all of the ideas for future research on TCE interesting, I was not convinced that all of the ideas, if executed, would have a significant impact in improving the risk assessment for TCE. It might be useful to triage these ideas into categories that identify them as crucial vs. merely interesting.

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

I did not note any technical errors or omissions. I found the Committee's report to be exceptionally thorough.

3. Is the Committee's report logical and clear?

I found the report to be logically presented and easy to follow. There was good consistency between the body of the text, the Executive Summary and the cover letter. I felt that the cover letter touched on the most important elements of the review, which I think is more effective than reiterating every aspect of the review.

There were only a couple of recommendations that I found difficult to understand. The Committee supported EPA's approach to use an array of endpoints as points of departure for the non-cancer risk assessment rather than a single critical effect, and provide good support for this decision on p. 42. The nature of the argument is that the RfD/C are similar for a number of endpoints and routes of exposure. However, the ensuing recommendation on p. 43 suggests that EPA base its RfD/C on only a few of these endpoints, excluding the renal effects. While there is uncertainty about dosimetry for the kidney effects, the robustness of the effect (vs. the "somewhat less confidence in the immune and cardiac malformation endpoints from a hazard identification perspective" (quote from p. 43 of the Committee's report)) would argue that the renal toxicity be retained as a critical effect in the risk assessment.

There is a recommendation to EPA that they speculate about the mechanistic role of immunotoxicity on cancer and other outcomes (p. 2, lines 8-10; p. 18, lines 33-38 and p. 19, lines 1-2). However, the Committee report also notes (p.16) that there is uncertainty as to the dose

levels at which immunosuppressive effects predominate over immune activation (e.g., increased inflammation). With this much uncertainty, it's unlikely that speculation about immune involvement in cancer progression or systemic toxicity would cause EPA to select a different risk assessment approach. Therefore, the requested speculation will neither change the approach or outcome of the assessment, nor add clarity to the report. The report already describes the literature on the immune effects of TCE, and these are taken into account in the non-cancer assessment.

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

I believe that the Committee's report is extremely thorough and that its conclusions and recommendations are supported by the text. The suggestions I make above are minor in nature.

Comments from Dr. Eileen Murphy

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

There were 12 charge questions with multiple subquestions within most of them. The report is organized around these questions.

1. PBPK Modeling
2. Meta-analyses of cancer epidemiology
3. Non-cancer hazard assessment
4. Carcinogenic weight of evidence
5. Role of metabolism
6. Mode of action
7. Susceptible populations
8. Selection of critical studies and effects
9. Derivation of RfD and RfC
10. Uncertainty factors
11. Inhalation unit risk and oral unit risk
12. Age-dependent adjustment factors

In the responses to EPA charge questions, the panel was very specific in their recommendations, even providing page numbers when addressing a particular issue. Each of the 12 charge questions had several related questions embedded within them. The Panel teased these apart and addressed each individually in an organized way, making it very clear and understandable.

All of the charge questions were addressed in detail. Just some minor comments on 3 of the charge questions:

Charge Question 4 not fully addressed. There were 4 subquestions within this charge question (page 20). The response to this charge question primarily focused on the first 2 – discussion of the epidemiological evidence for associations between TCE and cancers and quality of the meta-analysis. The reviewers did not discuss the laboratory animal data or the toxicokinetic much (mentioned on p. 20, lines 28-30 only). Some further discussion on these two issues needs to be presented.

Charge Question 6. Subquestions d and 3 – there is agreement that data are inadequate. However, would be desirable to hear if the panel thought that EPA had done “due diligence” in searching for data before they came to this conclusion.

Charge Question 11. The panel suggests some studies published before the report date of 2009. However, not sure if it is appropriate to include studies published after the report (after 2009), unless this represents inclusion of ALL appropriate studies published after 2009. Opens up the question as to what has been published and new interpretations AFTER the report was published in 2009. Maybe articles published after 2009 should be moved to charge question 12, where discussion of future assessments is made?

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

No.

3. Is the Committee's report clear and logical?

Yes, their recommendations are presented very clearly and logically.

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

Yes, conclusions are supported and fully explained and supported with literature.

Editorial:

Page 17, Lines 20-24 a different font is used in this bullet. Does not appear to be a reason for the different font, so assuming it is an error.

Page 24, Line 32, there is an underline at end of the sentence.

Page 31, Line 13. Period is missing at the end of the sentence.

Page 31, Line 15. Underline at end of the section header.

Page 44, Line 30. "h" should be in bold.

Page 51, Line 24. Fix the quotation mark before "However."

Comments from Dr. Stephen Roberts

The Committee was asked to review a large, multi-faceted report, and was presented with a long list of charge questions. Overall, the Committee report is excellent, with well thought out comments and recommendations clearly articulated.

Were the original charge questions adequately addressed?

Yes. All of the charge questions were adequately addressed. Although some of the responses are a little long, they read very well and are informative. I would not attempt to trim them simply to reduce the size of the Committee's report.

Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

None that I found.

Is the Committee's report clear and logical?

Yes. Responses are well written. I have only a series of editorial suggestions (below).

Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes. The recommendations are logical extensions of discussion provided by the Panel.

Detailed Comments

Editorial Comments

Pg 1, line 24, "needed"

Pg 5, line 18: something is missing ... "method of Raaschou-Nielsen et al." or "results of Raaschou-Nielsen et al."?

Pg 5, line 33, "provides"

Pg 6, line 22, "found that this"

Pg 6, line 24, change to "model improved the quality"

Pg 6, line 32, "along with the appropriate"

Pg 7, line 28, remove ")"

Pg 9, line 15, semicolon after "model"

Pg 14, line 1, replace "has" with "had"

Pg 15, line 28, "thorough but clear"??? This doesn't make sense.

Pg 17, lines 17-18: replace "so maybe they could be cited" with " and could be cited"

Pg 18, Editorial Comments: Put in same format as editorial comments with other responses.

These seem to follow the Recommendations.

Pgs 20-21. The flow of the first five paragraphs seems to be a little off, with some repetitive information. These could be tightened up a bit.

Pg 32, lines 18-19: delete "from which"

Pg 33, first bullet: The second sentence is confusing. Consider rephrasing.

Pg 38, line 28: “concluded that the approach used”

Pg 39, lines 30-38: It’s unclear how the bulleted points illustrate confidence in the PBPK approach derived from consistency in the RfDs and RfCs. A little more explanation may be needed.

Pg 45, line 30: suggest change to “provide more details”

Pg 52, lines 1-4: This material doesn’t seem to fit here.

Comments from other SAB Members

Comments from Dr. Ingrid Burke

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes. Each of the original charge questions seems to be addressed.

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

Because I am not in this field, it is quite noticeable to me when acronyms are not explained on the first use, requiring a serious search in the appendix. It needs some technical editing to get the acronyms named in parentheses after their first use, once in the executive summary, and again in the report.

3. Is the Committee's report clear and logical?

Yes. I would have benefited from a bit more context at the outset of the Executive Summary and of the report, on what the NRC recommendations were, and why a response was important. In addition, I think that the recommendations from the panel, and some of the key points (e.g. where the Panel disagreed with EPA) should be highlighted more clearly in the Executive Summary, using bullets, or some sort of style that sets them off as important to read.

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

Yes.

Comments from Dr. Terry Daniel

General comments

The SAB review of the EPA Toxicological Review on Trichloroethylene was commendably thorough and constructive and offered in-depth discussion of the 12 charge questions/areas posed by EPA. The many specific recommendations offered were finely focused and presented in sufficient detail to very clearly direct the revisions of the reviewed document. In several places the panel addressed important science issues that came up in their review that were not explicitly requested in the charge questions. The panel is commended for identifying these issues and for offering clear suggestions for why and how these issues should be addressed to improve the toxicological review and the scientific basis for the EPA's TCE risk management. This review evidences great effort on the part of the panel and their great dedication to improving the science of human health protection and risk management.

Quality Review Questions

1. YES: The original 12 charge questions to the SAB Ad Hoc Committee reviewing the EPA toxicological review for Trichloroethylene were adequately addressed;
2. NO: There do not appear to be any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. YES: Committee's report is clear and logical;
4. YES: The conclusions drawn and the recommendations provided are supported by the body of the Committee's report.

Comments from Dr. Costel Denson**Were the original charge questions to the SAB committee adequately addressed?**

Twelve charge questions were presented to the SAB committee for its review, with many of these consisting of a number of subsidiary questions. In effect, the committee was asked to address a total of forty-five (45) questions. The committee addressed each of these questions adequately and in considerable detail, providing useful insight and recommendations in every case. In instances where the committee did not agree with the draft IRIS document, the committee explained why and suggested possible remedies.

Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the committee's report?

Hazard and dose-response assessment (of trichloroethylene) is not within this reviewer's area of expertise.

Is the committee's report clear and logical?

The committee's report is laid out in a clear and logical way. Each charge question (and its subsidiary components) is presented and discussed, and the associated recommendations are presented with that particular question.

Are the conclusions drawn or recommendations provided supported by the body of the committee's report?

This reviewer cannot comment on this question because the subject is outside the reviewer's area of expertise. However, we note that the report contains nearly ninety recommendations.

Comments from Dr. David A. Dzombak

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

The charge questions appear to be adequately addressed.

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

I did not detect any technical errors or omissions, but I am not an expert in toxicology.

3. Is the Committee's report clear and logical?

I believe that the organization of the report needs some revision. Specific comments in this regard are as follows.

(a) The charge questions are not made clear in the Executive Summary. The charge questions are lengthy, but each could be reduced to a key question for inclusion in the subsections of the Executive Summary.

(b) The Table of Contents for the report should indicate that the body of the report (Responses to Charge Questions) begins on page 6.

(c) An Introduction section should be provided in the main body of the report, on page 6, prior to presentation of the detailed responses to the charge questions.

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

The conclusions presented in the letter and in the Executive Summary appear to be supported by the body of the report.

Comments from Dr. James K. Hammitt

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes. The highlighting of recommendations in each response is a nice approach, given the length of the report.

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

None that I identified.

3. Is the Committee's report clear and logical?

Yes, with the following exceptions:

There is apparent duplication of lines on p. 20 (30-34, 36-37) and p. 21 (22-24, 31-33).

p. 32 lines 24-27 seem to be a finding that should appear before the recommendations.

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

Yes, except the recommendation on p. 22 lines 27-31 does not seem to be supported by report (cancers of bladder, esophagus, prostate and cervix do not seem to have been discussed in the report).

Comments from Dr. Bernd Kahn

Concerning 'Toxicological Review of Trichloroethylene' EPA SAB review, the answer is 'yes' to all four quality review questions. The report is well done. Here are two minor corrections:

p. xi, 1.10: Insert '5. Role of Metabolism,,, 24'.

p. 38, 1.28: Insert 'the' after 'that'.

Regards,

Bernd

Comments from Dr. Agnes Kane

The SAB Panel presented a very detailed review of this report that adequately addressed the charge questions. No technical errors or omissions were identified. Despite the complexity of the scientific issues that were discussed very thoroughly, the recommendations were clear, succinct and well-documented. Consideration of non-cancer health effects was exceptionally complete as well as the discussion related to susceptible populations. The finalized IRIS document should be a high priority for EPA based on the serious health consequences of exposure to this chemical.

Comments from Dr. Madhu Khanna

1. Are the original charge questions to SAB adequately met?

The charge questions in my view have been 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;

To my knowledge there are no major technical errors or omissions.

3. Whether the Committee's report is clear and logical.

It appears to be clear and logical

4. Are conclusions or recommendations supported by the body of text?

The report is very comprehensive and its conclusions are supported by the body of the text.

Comments from Dr. Nancy K. Kim

I reviewed the trichloroethene report. It was really well done.

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes.

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

No.

3. Is the Committee's report is clear and logical?

Yes. I did find one paragraph that wasn't clear to me. It is on page 39, lines 30-38; it is the last paragraph under 8e. The paragraph begins with the words "Finally, as discussed further under sub-question (h)..... How the list of three dose-metrics meshes with the sentence preceding the list isn't clear.

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

Yes. I really like the format of the report.

Comments from Dr. Kai Lee

I have reviewed the SAB document that reviews the EPA draft assessment on trichloroethylene, and I support transmittal to the Administrator after the Board receives public comment. The SAB draft discusses matters beyond my own scientific knowledge, and I make no comment regarding the content of the SAB review.

Comments from Dr. Cecil Lue-Hing

I believe that all the charge questions were adequately addressed.

Rather than technical errors, there were some omissions and other deficiencies, mostly of clarification that were adequately dealt with in the Committee's report.

I find the Committee's report to be clear and logical

The conclusions drawn are supported by the text of the Committee's report.

Comments from Dr. L.D. McMullen

I think the charge questions were answered for what I know of the topic.

Comments from Dr. Judith Meyer

1. Were the original charge questions to SAB Committee adequately addressed?

This committee did a remarkable job of responding to 12 (!) complex charge questions.

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

Not that I could see, although this is outside my area of expertise.

3. Is the Committee's report clear and logical?

Yes

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

Yes

Comments from Dr. James R. Mihelcic

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

The original charge questions to the expert panel are adequately addressed.

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

I did not observe any technical errors omissions in the report.

3. Is the Committee's report is clear and logical?

The report is clear and logical and provides EPA with well defined recommendations on how to improve the report and appropriate literature that should be included. I have 3 minor comments that are listed below.

- a) The following sentence was not clear to me. On page 15 (line 28-29), I was not clear on this statement, seems like the wording should be "a thorough *and* clear description"

"In regard to the effects of TCE in the kidney, EPA had provided a thorough but clear description of these effects."

- b) In the following sentence, Page 17 (line 20), should the word "doses" be changed to "concentrations" or "drinking water concentrations."

"In Rufer et al. (2010), low doses of TCE (8 ppb) caused high mortality, functional cardiac"

In the following sentence on page 41, line 8, it was not clear to me if the two concentration values are correct, or if this is a conversion of units for a chemical concentration in the air (which in case should the temperature be noted?)

"As noted in the draft assessment, the proposed RfC, 0.001 ppm (5 ug/m³)"

- c) Page 57, line 38. Typo, word "et al" is spelled "et a;/"

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

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

Comments from Dr. Horace Moo-Young

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes. The original charge questions were adequately addressed by the committee. This report was extremely thorough and delves into great detail to address the charge questions.

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

No technical error or omissions in the report are identified.

Typo: page 35 line 11 wee replaced by were

3. Is the Committee's report clear and logical?

The committee's report is clear and logical.

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

I support the Panel's conclusions and recommendations. I am especially supportive of the recommendation to utilize a global sensitivity analysis approach for the PKPK modeling to strive to account for uncertainty analysis. A parametric analysis of modeling assumptions is highly recommended in the report to quantify the uncertainty.

Comments from Dr. Duncan Patten

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes, the panel report appears to respond in a very comprehensive fashion offering the reader a good understanding of its response. I was surprised that the report addresses typos and edits in an EPA document that, one assumes, will be rewritten and reedited.

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

This is outside my area of expertise to be able to answer this.

3. Is the Committee's report clear and logical?

The report appears to be clear and the use of breakout paragraphs helps with organization.

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

The conclusions and recommendations seem to follow clearly from the body of the report discussion, as far as this non-expert can tell.

Comments from Dr. Amanda Rodewald

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes.

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

No.

3. Is the Committee's report clear and logical?

Yes.

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

Yes.

Comments from Dr. Jonathan M. Samet

1. Were the original charge questions to SAB adequately addressed?

Yes, the questions were addressed.

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

Yes, generally, but see specific comments.

3. Is the Committee's report clear and logical?

Yes, the report is well written.

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

Yes.

Specific Comments

Page 1, lines 43-44: The comment about meta-analysis as written here is confusing, though better explained subsequently.

Page 2, lines 19-20: This would be better phrased that the animal and toxicokinetic data provide a biological basis for supporting the plausibility of the epidemiological findings.

Page 5, lines 13-16: I agree that the rates should be compared. Is there any reason to question the transportability of the risk estimates from France to the US?

Page 13, lines 16-19: I agree that bias is of concern in any epidemiological study. The terminology used to describe bias is non-standard and needs correction. I am not certain as to the meaning of "case-response bias"; differential information bias? selection bias? Also, selection bias might arise from the processes leading to participation by either cases or controls; the language should be clarified. With regard to cohort studies, drop-outs can lead to selection bias.

Page 21, lines 10-11: This statement with regard to exposure assessment is far too sweeping and not correct. Is the comment made with regard to studies of TCE specifically?

Comments from Dr. James Sanders

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes. The Panel adequately addressed the charge questions.

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

None that are apparent to this reviewer.

3. Is the Committee's report clear and logical?

For the most part. I have two suggestions that may help to improve the readability and utility of the report. First, the Executive Summary contains many acronyms. Many of them are not spelled out, however, when used for the first time. Although the report contains a listing of abbreviations and acronyms, because the summary may be read separately from the rest of the report (or may be the only section read), it would help greatly if the Panel ensures that this section defines each of the acronyms used. Ironically, in some cases (e.g., POD on p4), the acronym is defined, more than once. I recommend that this section be carefully edited to improve its readability.

Second, the main body of the report (beginning on p. 6) begins with the first charge question. I recommend that the Panel first include a short introduction, to set the context for the reader. A combination of the first two paragraphs from the letter to the Administrator, plus the first paragraph of the Executive Summary, would likely provide all that is necessary for this introduction.

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

Yes, the Panel's recommendations are well supported.

Comments from Dr. Kathleen Segerson

1. Are the charge questions adequately met?

Yes. The set of charge questions is very detailed, and the panel has responded to each one (including each individual sub-question) in considerable detail. The report is very responsive to the charge questions.

2. Are there any technical errors or omissions?

Not to my knowledge.

3. Is the report clear and logical?

In general, the report is clear and logical. The letter to the administrator is more technical than the typical letter the SAB sends, but it is still clear and logical and, for the most part, understandable by a non-expert.

There was one place where I thought the report was unclear. On p. 3 of the executive summary it states “The Panel expressed concerns about the use of several candidate critical studies and effects, ...” Then on p. 4 it states “The screening, evaluation, and selection of candidate critical studies and effects used for the development of the RfC and RfD were sound.” These statements appear to be somewhat inconsistent. The body of the report (p. 40) suggests that the Panel agreed with the use of some studies but not others. Some clarification on this in the executive summary would be helpful.

4. Are the conclusions and recommendations supported by the body of the text?

Yes. However, there are several places where statements that are essentially recommendations appear in the text (rather than under the separate heading of “Recommendations” that is used in most part of the report), and likewise places where some conclusions are included in the “Recommendations” but not in the text.

Some examples of recommendations in the text:

- P. 39, line 27: “The Panel recommended that HEC_{50} ...”
- P. 46, line 20-22: “typically, larger type-I error rates are used...” I assume this is a recommendation to use a larger type-I error rate, although it is not explicitly stated as such.
- P. 47, line 44-45: “The Panel recommended that EPA clarify....”
- P. 51, line 33-34: “EPA should perform a global sensitivity analysis.”
- P. 52, line 3-4: “These assumptions should be used consistently....”

Some examples of conclusions that are listed under “Recommendations”:

- p. 32, bullet 1: “The Panel disagreed with the statement....”
- p. 33, bullet 1: “The wording in Section 4.10 was often not clear....”

In addition, some of the conclusions are rather weak, stating, for example, that EPA “could” do something, rather than making the stronger statement that “EPA should” or at least “EPA should consider” doing it. The word “could” (which is used in a number of recommendations) simply indicates feasibility of doing something, not a recommendation to do it.

Finally, stylistically, the recommendations are inconsistent. Some are full sentences (e.g., “EPA should....”), others are simply directives (e.g., “Add documentation”), while for others the recommendation is not explicit but implied (e.g., p. 31, “Graphical or tabular presentation....”). The report would read better with a consistent style for recommendations.

Comments from Dr. R. Thomas Zoeller

The following comments are provided in response to the 11/23/2010 memo by DFO Dr. Tom Armitage concerning the Quality Review of the SAB workgroup's document of the same date entitled, "*Review of EPA's Draft Assessment entitled, 'Toxicological Review of Trichloroethylene' (October, 2009)*". This memo asked contributing SAB members to specifically address the four quality review questions from the vantage point of our own expertise. These questions are:

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.

Overall, the SAB document is thorough, thoughtful, and very clearly written. Moreover, it is extremely well organized so that it presents the SAB members' analysis clearly within the context of the 12 charge questions. These questions focused on hazard assessment of non-cancer and cancer health effects, the use of a PBPK model for TCE and its metabolites for the derivation of a proposed oral reference dose (RfD), an inhalation reference concentration (RfC) for non-cancer endpoints, cancer weight of evidence classification, mode of action of TCE carcinogenicity, as well as inhalation and oral unit risks for TCE.

Quality Charge Question #1. Considering these many and diverse charge questions to the committee, it was important for them to produce a document that was overt in its attention to this detail and they have done a good job of that. In general, the only potential weakness was that because of this complexity, the review document opted for a tiered approach whereby the same information is presented in summary form early and in greater and greater detail later. This strategy would be greatly enhanced if the details were indexed in the early summary statements. This would allow the reader to quickly navigate the document and obtain the greatest amount of information. Inasmuch as this reviewer cannot fully determine whether the charge questions were adequately addressed without studying the original EPA IRIS review, this document appears to have very thoroughly and expertly addressed these questions with a considerable amount of expertise.

Quality Charge Question #2. This reviewer did not detect any overt technical errors or issues that were incompletely or inadequately addressed. It is not possible to determine fully whether omissions were made, but there were certainly no omissions relative to the original charge questions themselves.

Quality Charge Question #3. Some of the language in the early part of the document is vague, but these issues are more fully developed in the later part of the text as discussed under charge question #1. It would be useful to index this so that the reader could obtain higher resolution discussion in the early part of the document.

Quality Charge Question #4. There are a series of recommendations made that are non trivial to carry out. These recommendations are well supported in the SAB review and clearly articulated. It seems clear that responding to these recommendations will considerably improve the EPA IRIS review for TCE.