

**U.S. Environmental Protection Agency  
Science Advisory Board  
Dioxin Quality Review**

**Pre-Meeting Comments from SAB Members**

Developed in preparation for the June 6, 2011, teleconference of the chartered SAB for quality review of the draft SAB report, *Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*

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## **Lead Reviewer Comments: George Daston**

Overall, I found this report to be well written, with the recommendations well supported. The dioxin report is voluminous and the review group is to be commended for its thoroughness in reviewing, comprehending, and making constructive recommendations.

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

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

I believe that all the charge questions were adequately addressed. There are two instances in which I would like to see the committee take a more definitive stance:

Given the committee's conclusion (p. 34) that the mode of action for dioxin is "reasonably well known" and the recommendations (p. 35) to thoroughly discuss the literature supporting a non-linear mode of action for the receptor-mediated effects of dioxin, it seems to me that the committee is expressing its preference for a non-linear extrapolation. I would like to see this stated explicitly.

The critique of EPA's decision not to do an uncertainty analysis at the end of the report is comprehensive, but does not really take a stand on whether the cost and time of doing it are worth the effort. The committee poses a number of very good questions on p. 47. Should it consider limiting its recommendations to addressing these questions rather than a more comprehensive assessment?

### **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 found no technical errors or omissions in the report. I have a few recommendations on technical matters for the committee to consider.

I believe that the committee should strengthen its recommendation on p. 39, line 27, regarding the use of dioxin-like compounds. There is a wealth of literature on these compounds that will add to the weight of evidence that can be used to support mode of action determination, as well as the plausibility of individual biological effects that are used as the basis for risk assessment. The committee does recommend that studies with dioxin-like compounds be used in this way on p. 16 (second reco.) but this is disconnected from the mode-of-action discussion.

The discussion of the Hill coefficient on p. 21-22 is interesting, but does not seem to be to be crucial to the dioxin assessment. For the sake of simplicity and plausibility, would it not make sense to use a value of one?

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

I found the report to be clearly and logically presented. My main concern about logic and clarity is in how to advise EPA to present a voluminous amount of information in a transparent and

readable way. The committee recommends twice (second bullet on page 12, first bullet on p. 15) that EPA get a technical editor to make major revisions to the document. Given that the report is 690 pages with a 1000+ page supplement, perhaps the committee recommend that something longer than an Executive Summary but shorter than a full report be written that captures the highlights of the response.

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

I found the conclusions of the report to be well documented and supported. There are only two issues that concern me.

The committee recommends (p. 17, lines 1-2) that EPA consider deleting “outside the range of normal variability” when discussing animal studies. Considering the historical control data, both for animal studies and in the clinic, is accepted practice and is crucial for interpreting toxicology data. In fact, the non-cancer critical effects for calculating an RfD both rely on an understanding of the range of normal to conclude that the effects on sperm count or TSH concentration are adverse. I think this recommendation should be reconsidered.

P. 28: I am less comfortable than the committee that the 20% decrease in sperm count and 11% decrease in sperm motility is biologically significant, especially given the limited number of samples obtained and analyzed. In addition to the recommendations given at the top of p. 29, please also consider recommending that a thorough evaluation of the strengths and weaknesses of the study be presented, along with the plausibility of this effect from animal studies. It is also important to fully explain the practical effect of a 20% shift in the mean for fertility of the population.

## **Lead Reviewer Comments: Steven Roberts**

### **1. Were the original charge questions to the Panel adequately addressed?**

For the most part, charge questions were adequately addressed. Some additional work may be needed on the response to charge question 4.2a.ii (page 28). It does not appear (at least to me) that the response specifically answers the question posed. The response to charge question 5.3 also does not appear to include a direct answer to the question. The brief response to charge question 5.5e may or may not be on target. It's difficult to tell, because the charge question itself is vague ("Please comment on this extrapolation.") The question could be interpreted as inviting comment on the appropriateness of linear versus non-linear extrapolation. If so, additional comment to encourage presentation of both types of extrapolations to be responsive to NAS recommendations would appear warranted.

### **2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

I found no technical errors or omissions. In general, the issues raised in the charge questions were adequately addressed, although some clarifications and perhaps expanded discussion are needed as noted in my other comments. There are some points that perhaps deserve more emphasis. Probably the most important of these is Panel opinion on the extent to which the EPA report is responsive to NAS comments dealing with a possible non-linear dose-response relationship for TCDD. Inadequate consideration of a possible non-linear dose-response relationship was one of the principal criticisms of the NAS in their review of the 2003 EPA exposure and human health reassessment of dioxin. The Panel identified treatment of this topic as one of the two main shortcomings in the current report under review (as highlighted in the Panel's cover letter to the Administrator), although comments in support of this opinion are relatively brief. In comparison, treatment of the second major shortcoming – the absence of a quantitative uncertainty analysis – is more robust. The Panel's position is abundantly clear and well described, with several constructive suggestions for conducting a quantitative uncertainty analysis. I encourage the Panel to take another look at the draft report from the standpoint of making sure that key points on the most important issues are appropriately emphasized.

### **3. Is the Panel's draft report clear and logical?**

In general, the draft report is clear and logical. Additional clarification is needed, however, in the following responses and recommendations.

Response to 2.2/2.3: The initial response states, "The Panel found that the EPA's study criteria and considerations were scientifically justified and clearly described ..." and that the Panel's major concern was clarity in regard to decisions to include particular studies or group of studies. This seems to be contradicted by the remainder of the response, which indicates that criteria should be made stronger, and that there is room for further clarification and justification. One of the recommendations begins, "EPA should further clarify the justifications for study inclusion and exclusion criteria/considerations." From these points, it seems that the Panel did not in fact think that the criteria were well justified scientifically or clearly described.

Recommendation in response to 3.4: This recommendation is a little vague. It should be expanded somewhat to capture the point about determining sensitivities under the same exposure conditions as those for which dose metrics were calculated.

Response to 5.5b: The response states simply that all-cancer mortality is an appropriate basis for the OSF “because of the extensive dose-response information.” The basis of this reasoning is not obvious to me. This is an important question that merits additional discussion.

Response to 6.1: Much of this response really pertains to question 6.2 (i.e., EPA’s decision that an uncertainty analysis is not feasible). This text should be moved and integrated into the response to 6.2 to avoid redundancy.

#### **4. Are the conclusions drawn or recommendations provided supported by the body of the Panel’s report?**

The conclusions and recommendations are supported by the body of the Panel’s report. The format of listing the question, the Panel response, and the Panel recommendation(s) works well, and helps to clearly identify the basis for the recommendations. I note that recommendations in response to charge questions 4.3 – 4.8 are contained in the response and not separately listed as in the rest of the report. It’s possible, given the format of the document, that the casual reader might miss them. If the Panel considers them important, they should be bulleted out in separate sections on Recommendations, as elsewhere.

Editorial comments:

Pg 12, lines 37-38, “... revised to generally indicate how this issue was considered.” The recommendation is vague. Perhaps it should be modified to state, “... revised to provide an overview of reasons why studies were excluded.”

Pg 15, line 35, “... presented in a scientifically sound manner.” The question asks if they were applied in a scientifically sound manner. If “applied” cannot be substituted for “presented,” I suggest dropping this from the end of the sentence.

Pg 22, lines 9-10. Citing specific public comments is unusual. Consider revising to simply note this point was raised in public comment.

Pg 31, lines 8-9, “... relevant to establishing and strengthening the proposed reference dose.” As a minor suggestion, consider dropping “establishing and” from the sentence to make clear that biochemical endpoints have an important but secondary role in setting the RfD for this chemical.

Pg 32, line 25: “... justified discussion” ?? Consider re-phrasing.

Pg 35, line 1: Should be “compliments”

Pg 38, line 7, "... did not facilitate the process.": It's not clear what this means.

Pg 48, line 11, "... about the state of the world": Consider re-phrasing. This could be interpreted as condescending.

## **Lead Reviewer Comments: Paige Tolbert**

### **1) Are the original charge questions to the SAB Panel adequately addressed?**

#### **Response:**

The SAB Panel has done a nice job addressing the original charge questions posed to them by EPA. The Panel has provided a thoughtful and thorough response to each charge question and a number of helpful, detailed suggestions.

Given the large number of recommendations, it may be helpful to prioritize the recommendations more explicitly. Furthermore, given that the current EPA document is already over 1000 pages and is the product of over a decade of reanalyses and responses to reviews, I wonder if the Panel considered which recommendations are critical to implement prior to finalizing the current report, and whether some may be proposed as future or ongoing EPA activities beyond the finalization of the report through other mechanisms, e.g., to be published as on-line addenda or updates. I'm not sure of the legal/regulatory ramifications, but implementation of all the recommendations would appear likely to further prolong the process of finalizing the report several years.

### **2) Are there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

#### **Response:**

I did not find technical errors, omissions or issues that are inadequately dealt with in the report.

### **3) Are the Panel's report is clear and logical?**

#### **Response:**

Overall, I found the Panel's report to be clear and logical. The report effectively communicates the Panel's assessment of the draft report with respect to EPA's charge questions. The report is extremely well-written.

There is a lack of consistency in presentation style through the body of the report, however, which could lead to confusion about what is being recommended. There are three styles: 1) most frequently, details of the panel deliberations and rationale are included in "Response" section and any recommendations distilled or repeated in the "Recommendations" section; 2) sometimes a recommendation appears for the first time in the "Recommendations" section without any support in the "Response" section (e.g., line 6, p. 29); and 3) sometimes a recommendation appears only in the "Response" section (e.g., line 29, p. 29). I assume this is a result of different panelists taking the lead in drafting different parts, rather than an intentional strategy to convey, e.g., prioritization of recommendations. One consistent style should be used. For clarity, I prefer the first of the three styles, despite the inherent repetitiveness. It gives a concise list of suggested action items in the "Recommendations", with expanded treatment including supporting details and rationale in "Response." I suggest adhering to a consistent approach to

most effectively convey the recommendations. Furthermore, as indicated in my response to Quality Review Question #1, I suggest more consideration of prioritization of the recommendations.

In light of the dissenting opinion, it would be helpful to provide a more emphatic presentation of how the opinion of the rest of the panel contrasts with the views expressed by the dissenting panelist, i.e., direct refutation of the statements made by the dissenting panelist included in Appendix A. For example, the dissenting opinion refers to EPA transforming “a non-existing effect at occupational exposure levels into a risk at current background levels” – the evidence from occupational studies does not indicate a “non-existing” effect; rather, statistically significant associations with cancer mortality have been reported (cite the NIOSH studies).

The panel proposes the descriptor of the state of knowledge regarding mode of action for TCDD toxicity of “reasonably well known,” instead of “largely unknown.” The proposed terminology seems awkward – what would be “unreasonably” well known, and “well known” in the sense of a large number of people knowing the MOA or that the MOA is well characterized? Would “partially characterized” or “generally understood” be more apt? Since this is a critical descriptor, it merits more thought.

Additional editorial comments:

Add date of EPA draft report to text of letter to Administrator Jackson and introduction to report (i.e., May 2010 after title of EPA draft report.)

To sentence at line 28, page ii, add “dissenting” and replace “indicated” with “expressed the view” as follows: “One dissenting panel member, however, expressed the view that at best there is equivocal evidence for TCDD classification as a human carcinogen.” Also replace “indicated” in similar statement line 40, p. 33.

Line 32, p. 7: in explaining choice of all cancer mortality for cancer endpoint, add something along the lines of “and because in the case of TCDD there appear to be multiple targets for carcinogenic action.” Similar language in line 40, p. 37.

Line 21, p. 16: it is stated that “the recommendation does not indicate that the Panel suggests that a different approach to data set selection is needed,” but one of the recommendations is not to exclude studies that do not include a statement regarding TCDD purity, which would implicitly expand the number of studies meeting criteria for inclusion. This inherent contradiction should be removed.

Line 26, p. 26 and line 12, p. 27: The term “coherence of evidence” could be useful in the text suggesting that EPA describe the collective impact of studies, including the studies of DLCs.

Line 28, p. 28: Leading this sentence with “The Panel supports ... for determining relevant TSH levels,” is disconcerting as this section is on sperm parameters. Suggest rewrite as follows, “The Panel strongly suggests that further discussion of WHO reference values for male reproductive parameters be included in the Report, as was done for the relevant TSH levels...”

Line 20, p. 31: suggest “may be less pronounced” instead of “would be partly negated.”

Line 32, p. 40: Simon 2010 reference not included in citations.

Line 34, p. 41: “to” missing.

Line 14, p. 42: replace “uncertain” with “uncertainty”

**4) Are the conclusions drawn or recommendations provided are supported by the body of the Panel's report?**

**Response:**

The conclusions drawn and recommendations provided are supported by the body of the Panel's report. Overall, the Panel's conclusions and recommendations are scientifically sound and well-justified. The Panel did an excellent job on a difficult task.

## **Lead Reviewer Comments: John Vena**

Science Advisory Board (SAB) review of the Agency's draft report entitled *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* ("Report").

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

I extend my compliments to the Panel for the comprehensiveness and thoroughness of their review. In my opinion each of the six charge questions were adequately addressed. It is noteworthy that they developed well articulated responses and complemented them with very detailed feedback including two appendices including one with superb editorial comments and corrections.

### **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 can tell based on my expertise.

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

The cover letter is concise and the bulleted text very effectively highlights the major recommendations. The letter captures the sentiments of the full review report. The introduction on page 1 is excellent and there is a clear statement on page 1 of the deficiencies in the report.

The executive summary is well done and provides an excellent overview of changes in recommendations to the report based on responses to each of the charge questions. In the executive summary it would be helpful to the reader to state how each section relates to the response of each of the charge questions or to better label each of the headings noting the number and subpart of the charge question that is being discussed. Also the lettering of the responses on page 4 of the executive summary section 4 (charge question 4) is different than the numbering used in the body of the report (a in executive summary is charge question 4.1 in response). This lettering is used throughout the executive summary but it does not match the numbering of responses in body of review.

On page 3 in the top paragraph the panel recommendation for a qualitative discussion is stated but it would be helpful to also provide a brief justification for the recommendation.

On page 5 lines 4-5. A recommendation is stated but no justification is provided. A brief statement would be helpful. In lines 18-20 a discussion of is requested of high dose acute and low dose chronic and comparisons are requested. It would be helpful to briefly state in the exec summary the rationale for this request as it is carefully articulated on page 27.

Page 7 lines 9-11 a more specific recommendation or more carefully worded summary of the recommendation is needed.

Page 8 line 32—state of the world???

Page 8 line 38 briefly specify which EPA sensitivity studies are useful.

In the response to Charge question one especially on page 12 the panel has been appropriate to make recommendations to clarify the report.

Response to charge question 1.2 on page 13 and the recommendation needs clarification and more details. What does the panel mean by “more discussion and clarity on the exclusion of null epidemiologic studies?”

Charge question 2.2/2.3 recommendation on page 16. Clarify what specifically is meant by “qualitative discussion”.

The section on pages 17 and 18 *Considerations concerning selection of epidemiology studies* is very well done.

Charge question 3.1.b response and recommendation, page 20 lines 34 and 42. please specify which “other published models”

The responses to the remaining charge questions are very well written, detailed and clear especially response to charge questions 4.1, 5.2, and 6.1 (pages 42-47 are extremely well done).

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

Yes. In my opinion the report is very well written, comprehensive in responses to the charge questions and is well referenced.

## **Comments from Ingrid Burke:**

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

Yes, quite clearly.

### **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 can see.

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

The report is clear and logical and very well organized. My comment about the clarity is that the recommendations are not all directly targeted on improvements or changes to the EPA response document, but rather, seem to recommend additional analyses or work do be done outside of the report. It seems to me that all the "recommendations" should focus on the report, and "responses" can clearly say what other work needs to be done, and make note if the work is outside the purview of EPA revising their response to the NAS report.

Charge Question 1 and 2 recommendations all focus on the report, the writing, the organization, and the clarity, as well as more discussion and sometimes more thinking and reporting on a topic.

Responses to Charge Question 3.1 recommend more "efforts to fully characterize the uncertainty", which I think means additional analysis; Charge Question 3.2 recommendations include peer review of the mouse model (not really within the scope of the EPA report, is it?); and recommendations for CQ 3.4 include a sensitivity analysis that I am not sure is to be included in the EPA report at this time.

(I have just noticed that there are sections under Charge 4 that include long responses but no clear and pithy recommendation).

There are similar sorts of issues under Charge Question 6.1.

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

This is one of the most critical reviews of an EPA document from the SAB that I have read yet. There are a lot of recommendations for changes in the report, additional analyses, etc. Despite this, much of the report begins with constructive summary comments, the diplomacy we use when writing tough reviews. However, my sense is that this report might be a little overly diplomatic. As an example, on page 11, the review begins by saying the report is clear and logical...then proceeds with many paragraphs related to descriptions of what must be lack of clarity (recommending changed grammar and syntax, reducing redundancies, use of better glossary material, etc). It seems to me that this occurs throughout the report. I suggest integrating caveats into the initial "good news" portion, and/or shortening/diminishing the impact or length of the criticisms. Probably the former is more appropriate.

## Comments from Terry Daniel:

### General comments

The Panel has presented clear and detailed advice to EPA regarding needed revisions in the Reanalysis document. The recommendations seem to be well-founded on the body of the Panel's review and importantly specific reference is made to several issues raised in the sizeable public response. The bottom line seems to be that the EPA should revise the Reanalysis documents especially by giving greater attention to non-linear model options, by completing and reporting a more comprehensive quantitative uncertainty analysis and by expanding and thus strengthening the basis for weight of evidence discussions. It is important to note that these revisions could, and should, help to address public concerns with the current document.

### Specific Quality Review questions

**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?**

It would appear so, though this reviewer does not have the requisite expertise to make that determination.

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

Yes, the Panel has provided a very well organized and readable report with clear and specific recommendations for EPA.

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

Yes.

## **Comments from Costel Denson:**

### **General Comments:**

The information in the body of the report, and in the executive summary, is nicely organized, especially so considering the large amount of information and detail that is incorporated. Six charge questions were presented, many with auxiliary sub questions. A response was provided for each question or sub question and appropriate recommendations included. All the information in the main report was sensibly reduced in constructing the executive summary, which is a bit lengthy, but needed. The letter to the Administrator is well framed in capturing the important points. There is one editorial issue in that letter in line 23, p.iii. Does the word “unfeasible” exist?

### **1. Were the original charge questions to the Panel adequately addressed?**

There are six charge questions, with subparts. All were adequately addressed.

### **2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel’s report?**

There are no technical errors or omissions that this reviewer is aware of

### **3. Is the Panel’s draft report clear and logical?**

Yes.

### **4. Are the conclusions drawn or recommendations provided supported by the body of the Panel’s report?**

They seem to be, but this reviewer is concerned that there is not unanimity of view in the committee on the role that Dioxin plays in carcinogenicity.

### **Comments from Bernd Kahn:**

I have read the subject draft report; my responses to the four questions are:

- 1) Where the original charge questions to the Panel adequately addressed?** yes,
- 2) Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?** no,
- 3) Is the Panel's draft report clear and logical?** yes, and
- 4) Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?** yes.

I have the following suggestions for the SAB review:

p.5, l.15: Insert 'found in the study at the city of' before 'Seveso' to clarify the subject

p.5, l.42: Maintain consistency for the units of 'microU/ml' here compared to 'u-units' on p.29, l.32.

p.6, l.38: Insert comma behind 'Report'.

p. 11-12: The system followed by the Panel of distinguishing between 'Response' and 'Recommendation' is effective except that it leads to frequent repetition, which should be corrected. Examples early in the draft report are 'it is not a trivial matter' on p.11, l.40 and p.12, l.35; and 'The report is long and dense' on p.12, l.1 and p.12, l.40, but this type of repetition occurs throughout – e.g., p.48, l.32-33 and p. 49, l.3-4 -- and should be deleted, possibly by making the Response shorter.

Similarly, the Panel has a tendency to explain the charge question before presenting it, as on p.11, l. 5 for the charge question on line 12. This is unnecessary here and on several subsequent occasions; deleting or shortening this introduction would save space and reading time.

p.48, l.40-41: Replace 'whatever uncertainty analysis EPA elects to undertake' with 'the recommended uncertainty analysis.'

## **Comments from Nancy Kim:**

The Panel's report is very well done, especially considering an extremely large and complicated document. The members are to be congratulated.

### **1. Were the original charge questions to the Panel adequately addressed?**

For the most part yes, although a few places mentioned below could be more direct.

In a couple of places, the Panel makes statements such as "It would be useful" (p. 5, line 17 and p. 27, line 40), "It would be important to determine" (p. 27, line 44), "Panel strongly suggests" (p. 28, line 30), "It would be appropriate to indicate" (p. 28, line 38), "it would also be useful" (p. 32, line 41), and "it might be helpful" (p. 33, line 4). If the Panel wants to be sure these and any other statements are addressed, they should be recommendations.

On p. 29, line 37, the Panel may want to add a statement that directly answers the question (e.g. the Panel agrees with EPA that the change in TSH levels reported...is a LOAEL, if this interpretation of the Panel's position is correct).

On p. 36, the Panel doesn't appear to answer charge question 5.3 directly.

### **2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

None that I detected.

### **3. Is the Panel's report clear and logical?**

Yes, for the most part.

I read the body of the report before I read the letter to the administrator and the executive summary. Reading the body of the report gives a different impression of the seriousness of the Panel's comments than what the letter or the executive summary does. Having detailed, scientific comments may highlight concerns that do not come through in the shorter summaries of the report. The scientific details do not belong in the shorter forms; however, the Panel may want to see if changing some of the language in the shorter forms would increase the consistency in connotation among the three parts of the document. If the shorter versions provide the correct impression, some slight revisions to the body of the report may help with consistency.

#### Executive Summary

Summaries of some of the responses to charge questions in the executive summary seem to provide different information than in the body of the report. For example, p. 4, line 44 states that "The Panel agrees with EPA's assertion that traditional (e.g. immune, endocrine, reproductive) endpoints are more appropriate than biochemical endpoints for establishing points of departure (PODs)." This is a very broad statement. The body of the report stated that biochemical

endpoints may be acceptable endpoints to establish PODs (p. 30, line 44), but agreed that for TCDD traditional endpoints are more appropriate (p. 31, line 2).

Another example is on p. 2, line 25. The executive summary states "...EPA had applied...criteria considerations in a scientifically sound manner." The body of the report agrees with the criteria, but I didn't see where it stated that the criteria were applied in a scientifically sound manner.

#### Body of the report

This comment is about the first part of the response to Charge Question 4.1, specifically statements on page 25, sentence beginning on line 42 ("The rationale...determining the RfD."); last sentence in this same paragraph (page 26, line 9-10); and sentence beginning on page 26, line 15 (However, in isolation from...setting the RfD). The first paragraph agrees with the selection of the two studies for determining an RfD and says that their strengths are described well. The last sentence in the paragraph states that their strengths and weaknesses need more discussion. Do the strengths need more discussion? The next paragraph states that the studies were less useful for setting the RfD. After reading the second paragraph in the response, it isn't clear if EPA completes the Panel's recommendations or suggestions (the Panel may want to change some suggestions to recommendations), the Panel believes that the same studies (Mocarelli and Baccarelli) will end up being the best studies for setting the RfD. If not, the Panel's agreement that these are the right studies for determining the RfD would be inconsistent. The Panel may want to look at the language to see if some language changes may help clarify the intent.

p. 48, line 11. I am not sure what this statement means. It is also in the executive summary. "EPA should focus instead on uncertainties about the state of world and display the different modeling choices and the consequences of making them?"

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

Yes.

#### Minor comments

1. p.11, line 41. The meaning of the sentence "We therefore suggest that EPA do this in a way that provides only a general consideration of this issue," isn't clear. The implications of what the Panel's suggestion is clearer in the sentence written on p. 12, line 35-38.
2. p. 41, line 34. Insert "to" between ability and provide.
3. p. 5, line 42. Is there a typo in 5 uU/ml?

## **Comments from Cecil Lue-Hing:**

### **General Comments**

This is an unusual assignment for the SAB, or at least one that is different from many of the others received from the EPA. The General Charge to the SAB requested the SAB to review the EPA's (Reanalysis) report as an SAB function, and in addition, that the SAB provide comments on whether the EPA's (Reanalysis) report had objectively and clearly presented the key NAS recommendations on the earlier, EPA's 2003 Reassessment Report on Dioxin Toxicity.

The request that the SAB determine whether or not EPA satisfactorily revise/re-write the report as recommended by the NAS presents the unusual aspect. In addition, the EPA Reanalysis report was over 1100 pages.

The Panel has done an excellent job of reviewing the EPA report and has provided some thoughtful recommendations to enhance the quality of the report, and for the report to be more responsive to the NAS recommendations.

### **The EPA's Response to NAS**

The short answer is **yes**, the SAB found that the EPA has responded satisfactorily to many of the NAS's recommendations, and **no**, the SAB found that the EPA has not responded satisfactorily to some of the NAS's recommendations.

The Panel has provided recommendations to improve the clarity and responsiveness of the EPA's report.

### **.Quality Review Questions**

#### **1-Were the original charge questions adequately addressed?**

The charge questions for this assignment include a new item, a performance review of the EPA's response to a set of NAS recommendations associated with the EPA's report. Both the original charge questions and the performance review questions were adequately addressed. Recommendations and suggestions were offered to improve the context where they were requested or otherwise felt to be appropriate.

#### **2-Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Panel's report?**

Unable to offer an opinion.

#### **3-Is the Panel's report clear and logical?**

Yes, with minor exceptions as noted for the Transmittal Letter.

#### **4-Are the conclusions drawn and recommendations provided supported by the body of the Panel's report.**

Yes.

## **Specific Comments**

The Panel found that the NAS's recommendations a) to use both nonlinear and linear methods for characterizing cancer risk, and b) to conduct a Quantitative Uncertainty Analysis were not adequately addressed by the EPA. The Panel has offered recommendations to make the EPA report more responsive to the NAS comments and recommendations.

### **Transmittal Letter**

The Hill Coefficient – Both the SAB & public commenters criticized the EPA for using an “Hill Coefficient” of inappropriate value. Given the many references to the Hill Coefficient in the Panel's report it appears that the use of this (Hill Coefficient) is a critical issue in the field of toxicology and perhaps should be reflected/included in the Transmittal Letter to the Administrator. This is the opinion of a non-toxicologist.

### **Citations/References**

Based on a spot check, it was found that some references cited in the text do not appear in the Reference Section – some examples are:

Page 45, bottom of page

first bullet – Saltelli et al., 2000a,b; Frey & Patil, 2002.

third bullet – van Frassen, 1966, 1980.

**Comments from L.D. McMullen:**

**1) Were the original charge questions to the Panel adequately addressed?**

Yes. Most of the charge questions had multiple sub questions that were individually answered.

**2) Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

I'm not an expert in this area, but I did not find any errors or omissions.

**3) Is the Panel's draft report clear and logical?**

I thought the report was clear and logical. However, I did feel that the letter to the Administrator was a little long. I feel that some of the background information at the beginning of the letter could be eliminated. I think the bullets in the letter are good. I also feel the executive summary maybe a little long. Eight pages is a lot for the executive summary even though there are a lot of questions that need to be summarized. In the general report, I liked the organization with the charge question followed by the response and then the recommendations. However, there seems to be some redundancy in the response and the recommendations. For example on page 12, line 40 is redundant to line 1. I don't think line 40 or 41 are really needed.

**4) Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?**

I think that the panel did a great job in providing responses and recommendations that should be very helpful to the agency.

## Comments from Judy Meyer:

### 1. Were the original charge questions to the SAB Committee 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. The following are basically omissions that can be dealt with by simple editorial changes. I note that the Panel mentioned several issues on which they had taken public comments into account, which I consider a positive response.

p. 6, line 17: the statement on congenital hypothyroidism needs a citation

There is no mention of the dissenting opinion in the Exec Sum, although it is in the letter.

p. 9, line 7: That earlier SAB review should be cited.

p. 9, line 33: Given that some of the issues in the *2003 Reassessment* were not repeated in the *Report* being reviewed, it would be useful to note whether or not the Panel was aware of the material in the *2003 Reassessment* so that the reader is assured that recommendations for inclusion of additional information in the *Report* are not asking for something that is in the *2003 Reassessment*.

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

Overall, YES. I do have some suggestions for where clarification is needed or where there seems to be inconsistency.

p. 5, lines 42 & 45: Define  $\mu$ U; 6, 7: define  $\mu$  units; these definitions could be put in the initial list of abbreviations and acronyms. "unit" is a unit of measure?

p. 8, line 32 and p. 47, line 11: "uncertainties about the state of the world" sounds like what we discuss over the dinner table. What is meant by that phrase?

p. 14, line 39: This statement (noting EPA's "point-by-point evaluation of which epidemiological studies were included and excluded") seems to conflict with the recommendation that more discussion and clarity is needed in why null epidemiological models were excluded.

p. 16, line 22: It seems to me that the Panel's subsequent recommendation not to exclude studies that did not have a statement on TCDD purity will in fact result in a different approach to data set selection. At the very least, it would seem to result in inclusion of more data sets.

p. 21, line 44: "repeated with multiple values" -- add "of the Hill coefficient."

p. 24, line 10: The question and response talk about the Emond model, but the recommendation is about other models. There is an unexplained disconnect here.

p. 25, line 8: I presume it should be  $\mu$ U and not uU?

p. 26, line 9: The first part of the paragraph says the strengths are well described. Here a more complete discussion of strengths and weaknesses is called for. Those two seem inconsistent. Shouldn't it be just a call for further discussion of weaknesses?

p. 26, line 20: "A strong voice from the committee was given" -- this makes it sound like one person. Also I thought it was "the Panel" and not "the committee."

p. 29, line 32:  $\mu$  units rather than u units.

p. 31, line 6: This sounds like a recommendation, although it is not indicated as such.

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

YES

I found the very complete discussion of how EPA might do a quantitative uncertainty analysis to be particularly exemplary. Oftentimes Panels just tell EPA to do something without providing much guidance. This is an excellent example of backing up a criticism with some useful direction and literature references.

## **Comments from Keith H. Moo-Young:**

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

Yes, the charge questions to the SAB committee were addressed. The SAB committee commended the SAB Dioxin Report for the consistency, rigor and comprehensive nature of the written 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?**

Yes. There were some inconsistencies which were pointed out regarding methodologies and approaches utilized by EPA. First, the current report should potentially revise its recommendations regarding quantitative uncertainty analysis to specifically reference relevant EPA guidance that should be applied in conducting that analysis.

One public commenter pointed out that there are significant deficiencies in EPA's analysis of epidemiology data. In particular, three references were left out of the analysis of TCDD exposure which demonstrated no excess cancer mortality (Mundt et al. (2011), Cole et al. (2004), and Buffler et al (2011)).

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

Yes, the report is clear and logical. The report is extremely long. It was suggested that the report be written to consolidate the most relevant recommendations, and move some of the information to appendices.

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

Yes, the conclusions drawn and recommendations support the body of the committee's report. However, recent studies conducted by NAS on IRIS assessment for formaldehyde point out significant deficiencies of the IRIS process. NAS has provided a roadmap to correct these flaws. Since this report appeared after the initial review, I suggest that EPA acknowledge that this report has been written in the SAB report to the administrator. Thus, the SAB should make a recommendation to EPA to review the IRIS and determine if there are flaws/error/deficiencies and write an addendum to the report which could clarify any potential inconsistencies.

## **Comments from Eileen Murphy:**

### **1) Were the original charge questions to the SAB committee adequately addressed?**

Yes. This was a very well-written and understandable report. Charge questions were clearly delineated and 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?**

There were no technical errors or omissions apparent in the report.

### **3) Is the committee's report clear and logical?**

The report was well-written, thorough and easy to follow. One minor note: in the executive summary and in the body of the report, the Panel recommends that EPA consider alternatives to an intensive quantitative uncertainty analysis. It was not until page 45 that actual suggestions were made. As a reader, I thought the recommendation fell short by not providing specific methods. Earlier in the narrative, it should be stated that methods are recommended and presented.

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

- The report articulated the issues of the Panel members very well. However, there are instances where it is clear the Panel was divided. One example is the dissenting opinion. But the other apparent area is the recommendation regarding the quantitative uncertainty analysis. Because this document represents recommendations for EPA, the recommendations need to be very clear. The Panel presents a logical and meaningful discussion of this issue and EPA should be able to use the information provided to make their decision about 1) whether to pursue quantitative uncertainty analysis, and 2) which type of statistical approach to use in such an analysis. However, the narrative was sometimes contradictory. On page 43, it is noted that the Panel was not in consensus about the value of a quantitative uncertainty analysis in general. Yet, on page 47, the language is much stronger, stating that "...EPA should provide a thorough quantitative decision analysis that makes explicit the current uncertainties... without such quantitative analysis, risk management decisions for TCDD will not be adequately informed..." It shows that there was disagreement on this recommendation. It is difficult for the Agency to know what to do with this recommendation when the Panel itself was somewhat undecided.

Regarding the suggestions for alternates to an intensive quantitative uncertainty analysis, I'm not sure whether or not Bayesian methods are ready. While I agree that Bayesian methods can be powerful, these are still being researched for applicability as statistical approaches and need further testing to be truly useful in a regulatory framework. I think it would be an interesting scientific exercise but not appropriate for this analysis. I do agree that the other suggestion (i.e., sensitivity analysis studies) can be done without too much resources expense by the Agency and may strengthen the report.

- Another example where it seemed the Panel was not speaking with one voice concerned the recommendation to include exposure studies on dioxin-like compounds (DLC). On page 39, it is stated that the Panel was conflicted on use of DLC studies for dose-response estimates. I agree with the EPA *Report* that it is not desirable to incorporate the DLC exposures in the dose-

response modeling. It would be acceptable to include DLC studies in the weight-of-evidence analysis, though I think this would simply add a lot more work for little benefit in the end. Because regulatory standards are based on TCDD (i.e., clean-up standards, water quality criteria), I think it is appropriate not to include the DLC studies here. A decision to include the DLC studies would need to be justified. If EPA does include the additional studies, I suggest putting this information in an appendix.

- The recommendation for EPA to conduct an external peer review of the mouse model because it has not been published in the peer-reviewed literature goes beyond the purview of the charges. It would be fair to recommend that EPA use a peer-reviewed model, or present information indicating that peer-review is not necessary, But I do not think it is reasonable to ask the agency to conduct an actual external peer review of the mouse model. Edmond published the rat model in *Environmental Health Perspectives* and *Toxicological Sciences*, both of which are peer-review journals, and EPA used this rat model to develop its mouse model. Maybe rather than recommend a full external peer-review of the adapted mouse model, a comparison between the EPA mouse and Edmond rat model can be provided, indicating how it is appropriate for use here. A full peer review can take a year to conduct. Given that the first dioxin report was published in 2003, additional non-pivotal exercises may not be efficacious.

- I am confused by the recommendation to provide additional discussion for use of the Edmond mouse model. The Panel states that it agrees that the Edmond model provides “the best available basis for the dose metric calculations in the assessment.” Given that the Panel agrees with the selection of this model, why it is recommending more discussion of other published models and basis for selection?

- Throughout the report, the Panel recommends that the *Report* include more information about the studies that were not used. They also state that the *Report* is very long and that efficiencies need to be created. I suggest that additional information on the rejected studies be moved to an appendix rather than included in the body of the *Report*. This will prevent the document from becoming even longer and will address the recommendation of the Panel.

- Comment on dissenting opinion: The dissenting opinion reflects the expert’s professional judgment that low levels of dioxin cannot be carcinogenic based on occupational exposures that show equivocal associations between heavy exposures and cancer. There is no scientific evidence presented to demonstrate that this is the case. In fact, the Panel states on page 33 that “the available occupational epidemiologic studies provide convincing evidence of an association between TCDD and human cancer...). The dissenting opinion does not provide enough scientific justification to alter the general recommendations in the Panel’s report.

Editorial

p. 35, line 1, change “complements” to “compliments”

## **Comments from Duncan Patten:**

### **1) Were the original charge questions to the Panel adequately addressed?**

This is difficult to assess as to answer this one should have read both the EPA Report and the NAS Report which EPA responded to. It appears as though the panel has adequately addressed the charge questions.

### **2) Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

This is beyond my area of expertise.

### **3) Is the Panel's draft report clear and logical?**

There appears to be some contradiction in the panel's response to the charge question #1 dealing with clarity of the EPA report.

In response to this charge, the Panel says first that "EPA has developed a report that is clear, logical and responsive" (page 11), and then on page 12 last bullet the Panel says the "report is long and dense" and "would benefit from greater clarity in writing".... it seems to me that the Panel also needs to either say the EPA report is not clear and logical" or change its text.

This conflict also shows up in letter to Administrator (last bullet) where the Panel says the report needs "improved editing and restructuring.... to eliminate redundancies"...

### **4) Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?**

The Panel has made strong points supporting and suggesting improvements in EPA's report responding to NAS based on good evidence. Obviously, the Panel discussed the dissenting opinion of one Panel member, but has the Panel closely considered the concerns of some "public" comments?

**Comments from Amanda Rodewald:**

**1) Were the original charge questions to the Panel adequately addressed?**

Yes. Charge questions were addressed clearly and directly.

**2) Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

Because the topic is outside of my area of expertise, this is difficult for me to address. I am concerned by the issues highlighted in the letter to the Chartered SAB from the ACC. I would like to hear the panel's responses to each of the concerns articulated in that letter before answering this.

**3) Is the Panel's draft report clear and logical?**

Yes. At times, the report was repetitive, but this seems to reflect some overlap in focus of charge questions.

**4) Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?**

When reading the report, I felt that each recommendation was supported and the rationale clearly explained. However, I am concerned by several issues raised in the ACC letter.

**Comments from James Sanders:**

**1) Were the original charge questions to the Panel adequately addressed?**

Yes, the panel has provided clear discussion for each charge question.

**2) Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel's report?**

None that I am aware of.

**3) Is the Panel's draft report clear and logical?**

Yes, the panel's statements are clear, concise, and logical.

**4) Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?**

Yes.

## **Comments from Jerald Schnoor:**

I have read the entire report by the SAB Dioxin Review Panel, chaired by Dr. Timothy Buckley. Overall, I find the report to be well written and responsive to the charges from EPA. As requested, I am responding to the four quality review questions in greater detail below based on my reading of the document and some expertise in environmental fate, transport and exposure modeling.

### **1. Were the original charge questions to the Panel adequately addressed?**

Overall, I believe the report is responsive to the charge questions and easy to understand and comprehend. Answers to a few questions are somewhat vague or equivocal. It would appear that in these cases, the Dioxin Review Panel themselves shared some differences of opinion. For example, the Panel response to charge question 4.2.a.i is vague and does not answer the question directly (page 27, lines 36-44; and page 28, lines 1-10), although it does certainly “comment on EPA’s approach”.

The charge question 5.5e. on page 38 is not answered very thoroughly. The Panel simply responds very briefly on page 38 (lines 33-34) and then recommends that EPA should expand the discussion in the report. Some elaboration of what they want EPA to do would be better.

### **2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the Panel’s report?**

There were a couple of places that the report could be more explicit. For example, on page 21 (lines 21-27), the Hill coefficient does not carry any units and it is not very clearly defined. It may in fact be dimensionless, but it was a little confusing to me since the text discusses derivation of the Hill coefficient “based on fitting kinetic data”. If it has units associated with it, they should be given explicitly. Likewise, I believe the fat:blood partition should have units of mL/g (page 22, lines 1-2).

### **3. Is the Panel’s draft report clear and logical?**

I believe the Panel’s report is quite well written, clear and logical. However, in a few places, it is not perfectly clear what the Panel wants to say. For example, the discussion of Mode of Action (MOA) found on page 7 (lines 13-17) and page 35 (lines 30-40) seems to be one of semantics. Whether the mode of action for TCDD toxicity is “reasonably well known” or “largely unknown” is not the point. The Panel agreed that the “exact mechanism of action has not been full delineated for any distinct TCDD toxicity endpoint”, and this characterization of the question is much better stated than the dichotomy posed earlier.

In response to charge question 4.1, the Panel agreed that dioxin-like compounds (DLCs) should be included in the weight-of-evidence argumentation by EPA in their Report. The response on pages 25-26 is excellent, well-written, and compelling.

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

Yes, the conclusions and recommendations are well supported by references and logical arguments germane to the questions posed. For example, I agree with the discussion on Quantitative Uncertainty Analysis and thought it was well reasoned and written. In particular, the discussion on page 8 (lines 7-41) was well done.

The rationale for the response to charge question *3.1.a* was particularly cogent and convincing (page 19, lines 29-37). The Panel makes a compelling argument that blood should be the proper metric to be used in this case.

As a journal editor, I concur with the Panel regarding TCDD purity statements and their recommendations regarding rejecting studies without explicit statements (page 16, lines 27-40). Most authors do not make such explicit statements of purity because the scientific community because the commercial source of the exposure chemical is well known to be pure.

In response to charge question *5.2.a* on page 34 and 35, the Panel does an admirable job of laying out the case for why nonlinear modes of action should be considered in the Report, even if the linear model is ultimately chosen.

## **Comments from Kathy Segerson:**

### **1. Is the report responsive to the charge questions.**

Yes, it is very detailed and directly responsive.

### **2. Are there any technical errors?**

Not that I can identify.

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

Yes, but please see comments below.

### **4. Are the conclusions supported?**

Yes, but again please see comments below.

## **Comments:**

1. It is rather unusual to have a dissenting opinion (at least in my experience). This is mentioned in the letter to the administrator and the report itself, but I saw no mention of it in the executive summary (maybe I missed it). If it is important enough to be in the letter, it seems it should be in the ES. And I don't know what the standard SAB procedure is for dealing with dissenting opinions, but as a reader of the report I would have liked more discussion of the source of the disagreement or at least some response by the Panel to the dissenter's claim. I imagine this would be helpful to EPA as well if they are called upon to address this dissenting opinion.

2. I found the discussion of the linear vs. non-linear models somewhat confusing. The letter states that EPA "states that only a linear approach could be justified." But it is not clear if the Panel disagrees with this statement (i.e., thinks a non-linear approach CAN be justified) or is simply saying that EPA has not made its case sufficiently strongly. This is equally unclear in the ES. In general, the message here seems mixed and confusing, including the conclusion that "In the absence of a definitive nonlinear mode of action, a linear option can serve as the baseline for comparison with these other estimates."

3. I also found the conclusion regarding uncertainty analysis confusing. The letter states that the panel does not agree that a "unified quantitative uncertainty analysis" is unfeasible. However, the ES suggests that EPA's justification for this infeasibility is based on time and resource constraints. Since feasibility is always defined relative to constraints, it seems important to be clear about what the panel believes is or is not feasible given EPA's constraints. The ES (p. 8) seems to be suggesting that the panel agrees that a complete analysis might not be feasible, but suggests that there are other (more limited?) uncertainty analyses that might be feasible. So the question is whether there is disagreement about whether a *complete* analysis is feasible (it seems not) or just about whether, given that a complete analysis is not feasible, there is anything else

that can be done within the available time/resource constraints. Again, the message is confusing and some clarification of this would be helpful.

4. The ES is very long and, relative to most, quite detailed. In many places it essentially repeats the charge question, or summarizes the EPA report. It also includes a level of detail that is not typical in an ES (e.g., the editorial comments on p. 2, lines 34-39). By eliminating some of this, it seems the ES could (and should) be shortened.

5. The body of the report contains a large number of recommendations. If there is some way to identify in the report itself the distinction between “Major recommendations” and “other recommendations”, I think this would be helpful.

## **Comments of Thomas Zoeller:**

### **1. Were the original charge questions to the Panel adequately addressed?**

In general, this is a very well-written and well-structured SAB report that very clearly addresses the 6 charge questions to the SAB panel. These charge questions were clearly laid out and answered directly in the document.

### **2. Are there any technical errors or omissions in the report or issues that are inadequately dealt with in the draft report?**

This reviewer sees no technical errors per se, but I have a few comments that the committee may consider:

a. Page 3, last paragraph. The concept of the best dose-metric of TCDD is a practical one in reality, but the issue of tissue-selective uptake bears to some extent on this. While blood levels are likely to be the best dose metric, is it important to recognize that tissue uptake is non-uniform? Moreover, when one considers DLC's, their tissue distribution could be quite different from that of TCDD itself, so these may not be equivalent at all in their toxicity profile at a specific endpoint.

b. Page 6, line 10. The issues of "mild" or "subclinical" hypothyroidism, congenital hypothyroidism, and "transient" hypothyroidism (during development) have different literatures and it might be useful to discriminate clearly between these situations.

### **3. Is the draft report clear and logical; and**

In general the draft report is clear and logical. Perhaps the only issue that this review felt was not clear was the concept that the comprehensive data base of both animal and human epidemiological studies be used to demonstrate a "consistent and integrative signal of toxicity across species and endpoints for TCDD." There are several possible interpretations of this sentence, and it might be useful to find a clearer way of stating this.

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

The conclusions and recommendations are well supported by the body of the Committee's report.