

**Preliminary Comments from Members of the Chartered SAB and Board  
Liaison Members on the *SAB Report on the EPA's Responsiveness to SAB 2007  
Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic*  
(October 25, 2010 draft).**

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## **Comments from lead reviewers**

### **Comments from Dr. Jonathan Samet**

1. Whether the original charge questions were adequately addressed?

The SAB report responds to a total of three charge questions, each covering a topic needing in-depth coverage. In general, the report is satisfactory in addressing these three questions in responses that total 16 pages. I have no general concerns about the coverage.

2. Whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report.

I have a few minor comments around specific technical matters as follows:

The SAB suggests that EPA consider including an addendum or appendix describing major epidemiology studies published since 2007. The SAB report clearly acknowledges that continued updating of this effort is not practicable. In commenting on the potential utility of updating, the report comments "... EPA should consider including an addendum or appendix describing major epidemiology studies published since 2007 (i.e., those studies that can influence the dose-response curve due to large sample size or affect estimate that is substantially different than that estimated by Chen et. al." The IRIS Risk Assessments are notorious for the time needed to develop them. Here, SAB encourages an expansion that could lead to further delay. Additionally, the document does not offer any useful way to judge what studies might "impact the 2010 assessment." I caution against adding this appendix.

With regard to characterizing the Taiwanese dataset as coming from an ecological study, the document is correct. In this circumstance, given that the exposure is at the population level, the usual limitation of ecological assignment of exposure is less severe.

On page 6, lines 40-44, the document comments on issues related to power. Here, there seems to be confusion with regard to the range of exposure over which an effect is estimated and the absolute concentration spanned by that range. A restricted range within a study population will limit estimation, and studies carried out at a lower-level of exposure will be estimating an effect smaller than that at higher levels. Clarity is needed here.

On page 10, lines 23-25, the document addresses potential additional sensitivity analyses that might extend to strata defined by several parameters. Some guidance should be given as to the necessity for carrying out these additional analyses. The document reads as ambivalent.

3. Whether the committee's report is clear and logical?

Yes, the report is clear and logical, and well written.

4. Whether the conclusions drawn are recommendations provided are supported by the body of the committee's report?

In my opinion, the conclusions and recommendations are well supported by the discussion in the report.

## Comments from Dr. Paige Tolbert

The following comments are provided in my role as discussant/quality reviewer of the SAB Inorganic Arsenic Cancer Review Work Group's Review Comments on EPA's Draft Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System.

In reviewing the report by the SAB Work Group, the discussants are asked to respond to the following Chartered SAB quality review questions:

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

### **Quality Review Question #1: whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed.**

#### **Response:**

The SAB Work Group has adequately addressed the original charge questions posed to them by EPA.

The following questions constitute the original charge questions to the SAB Work Group:

Work Group Charge Question #1. Please comment on EPA's response to the recommendations and the conclusions of the SAB (2007) Arsenic panel regarding the evaluation of the epidemiological literature.

Work Group Charge Question #2. Please comment on EPA's response to the SAB's recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.

Work Group Charge Question #3. Please comment on EPA's sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.

I will comment on the adequacy of the Work Group's response to each of these charge questions in turn.

Regarding Work Group Charge Question #1, the Work Group concluded that the EPA had been responsive to the SAB 2007 recommendations in evaluating the published epidemiology studies,

and concurred with the choice of the Taiwanese dataset as the most appropriate data to use in the risk assessment. Further, the Work Group expressed some concern regarding EPA's presentation of the review of the epidemiologic studies and provided specific recommendations regarding how the evaluation could be improved. The Work Group adequately addressed Charge Question #1. It is well-justified in finding that the EPA was responsive to the original SAB recommendations regarding review of the epidemiologic literature and in finding that the Taiwanese data continue to provide an appropriate basis for the risk models. The Work Group found that the draft IRIS report presents a comprehensive overview of the epidemiologic literature, and is responsive to the 2007 SAB recommendation that a specific set of issues (the eight items listed on page 5 of the Work Group draft report) be reviewed in evaluating the studies. Moreover, the Work Group is on target in indicating that the review of the epidemiologic literature would benefit from additional work. As pointed out by the Work Group, EPA needs to more clearly state the criteria used in evaluating studies and present the review in a more systematic and synthetic way; this will make EPA's choices regarding data used in the risk models more transparent and compelling. While it is always difficult to extract a uniform set of descriptors from the various studies comprising the body of literature on a topic, the Work Group is correct in pointing out that Table B-1 would benefit from further work. It does not consistently convey the most important information about each study, such as sample size (for each exposure grouping if available), the estimate of effect (e.g., RR) and associated estimate of stability of the estimate, and expected biases. Furthermore, the text evaluating the literature in Chapters 4 and 5 of the IRIS report needs additional synthesis summarizing the relative merits of the studies to increase transparency regarding the ultimate decision to rely on the Taiwan data. For instance, a qualitative judgment of the relative bias to the null resulting from lack of individual exposure estimates across different studies could be provided (e.g., might this be expected to be a greater bias where people drink more bottled water and have higher residential mobility?) The current draft report has resolved several minor issues that were present in the earlier draft. Overall, this reviewer concurs with the Work Group assessment in response to Work Group Charge Question #1.

Regarding Work Group Charge Question #2, the Work Group found that EPA was responsive to the 2007 SAB review in performing requested sensitivity analyses of the dose-response modeling and concurred with the EPA rationale for choosing a linear low-dose extrapolation risk assessment approach. The Work Group suggested that EPA acknowledge the complexity stemming from multiple potential mechanisms and targets of arsenic carcinogenicity and the limited understanding of the mode of action, supporting the default choice of a linear approach for risk assessment. The Work Group agreed with EPA's assessment that for the most part the various sensitivity analyses performed did not materially change the estimated risk levels. For one case where the sensitivity analyses yielded materially different risk estimates, i.e., the sensitivity analysis incorporating a reference population, the Work Group requested that additional information be incorporated into the IRIS report from the relevant 2005 issue paper and the Work Group suggested that EPA further address this issue. The Work Group further requested additional description of the Taiwan data to make the IRIS report self-standing, and publishing the data and parameter tables used in its modeling analysis for greater transparency in the presentation. This reviewer finds that the Work Group response to Charge Question #2 is adequate. The reviewer agrees with the Work Group's assessment that EPA was responsive in performing sensitivity analyses and that EPA was justified in its use of a linear low-dose

extrapolation in its risk assessment. As the Work Group emphasized, the linear model is the prudent choice given lack of compelling evidence of a threshold or other dose-response form. The Work Group request for further work and expansion of the IRIS report as described above is also well justified.

Regarding Work Group Charge Question #3, the Work Group found the EPA Draft IRIS report was partially responsive to the 2007 SAB review. With respect to the sensitivity analysis of the impact of drinking water consumption and non-water arsenic intake assumptions on the estimated cancer potency, the Work Group found the approach to be minimally adequate, and recommended that EPA expand its treatment of this issue with more explanation of the observed sensitivity to the non-water intake assumption in one subgroup, better justification of the default assumptions regarding drinking water consumption and non-water arsenic intake rates, more description of how village well measurements were used in the water concentration assumptions, more complete presentation of sensitivity results, possible consideration of sensitivity to selected sets of exposure assumptions, and explanation of the rationale for not including some of the analyses suggested by the 2007 SAB review. This reviewer finds the Work Group response to Charge Question #3 adequate. The Work Group provides the basis for the finding that the EPA report is partially responsive, and provides detailed suggestions for how the EPA report could be improved to be more responsive to the original SAB input and to increase transparency.

**Quality Review Question #2: whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report**

**Response:**

This reviewer did not find technical errors, omissions or issues that are inadequately dealt with in the current draft of the report. Minor technical concerns with the earlier draft of this report have been addressed.

This reviewer has some remaining concern about the Work Group recommendation to summarize major studies since 2007 (p.7). To make the judgment that selected studies are major and have a potential impact on the risk assessment would require careful deliberation of the body of new studies, which could lead to a substantial delay. A quick review highlighting important developments could be helpful, but doing this in a cursory way could lead to the process becoming mired in debate. This reviewer feels that EPA should be given wide latitude in determining whether to pursue this option. In the revised report, the Work Group did clarify that if such a review is undertaken it should be restricted to those studies that can influence the dose-response assessment due to large sample size or substantially different effect estimate.

**Quality Review Question #3: whether the Committee's report is clear and logical**

**Response:**

As described above, this reviewer finds that the Work Group's report is clear and logical. The report effectively communicates the Work Group's assessment of the draft IRIS report with respect to EPA's charge questions.

**Quality Review Question #4: whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report**

**Response:**

The conclusions drawn and recommendations provided are supported by the body of the Work Group's report. As described in response to Quality Review Question #1, the Work Group provides ample rationale for its recommendations. The Work Group has chosen not to expand its review beyond the narrow scope of the original charge questions. With respect to the original charge, the Work Group's conclusions and recommendations are scientifically sound and well-justified.

## Comments from Dr. John Vena

Revised draft report from the SAB Work Group to Lead the Review of the Arsenic Cancer Assessment entitled *SAB Report on the EPA's Responsiveness to SAB 2007 Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic* (October 25, 2010 draft).

1. Whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;

The SAB Arsenic Cancer Workgroup in my view adequately addressed each of the three charge questions.

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;

There are several instances where the cover letter and Executive Summary do adequately capture the sentiment of the statements in the body of the text responding to the charge questions. Also there are several statements and recommendations that need to be clarified as noted below in specific comments

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

Yes except for the recommendation in response to Charge Question 3 on page 14 for testing the effects of layered assumptions. It is not clearly stated why it may be instructive to examine selected sets of exposure assumptions.

Response to Charge question 1:

Page 6 lines 10-16 request clarification and format changes. This recommendation should be more clearly stated in the cover letter (page 1, line 38) and in the executive summary. On Page 6 line 14 it is not clear what "pulling any essential information from references into the text" is meant to convey.

Page 6 lines 44-46, the recommendation that "the summaries of the epidemiology studies should include a quantitative presentation" is vague. Are they recommending a formal meta-analysis?

This recommendation is also vague in the cover letter and executive summary.

Page 7 lines 11-17 should include statements regarding differential versus non-differential bias. More specific justification for recommendations for estimating the quantitative consequences of bias should be provided. Would such an exercise change the conclusions of the document?

Page 7 lines 25-33. Should the SAB specifically recommend that the literature published since 2007 be incorporated in the updated risk assessment?

### Response to Charge Question 2

Page 9 lines 37-41. It is not clearly stated why the variability of well measurements needs to be presented to assist in understanding the results of the sensitivity analysis.

Page 10 line 8-10. How will more information on the variability in the underlying water concentration data help substantiate the reported models and results?

Page 10 Lines 27-37. This paragraph seems to be unwarranted and I recommend that it be omitted. The paragraph is much better worded than the confusing statements in the cover letter (pg 2 of cover letter lines 22-24) and Executive summary page 2 lines 29-31. These should also be omitted.

### Charge Question 3

Page 16 lines 1 and 2, clarify the statement that “assumed values take on a life of their own and the evidence on which they are based is lost”.

## Comments from Dr. Thomas Zoeller

The following comments are provided in response to the 10/25/2010 memo by DFO Dr. Angela Nugent concerning the Quality Review of the SAB workgroup's document of the same date entitled, "*Review Comments on EPA's Responsiveness to SAB 2007 Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic*". 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.

Quality Review Question #1: whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed.

The following charge questions were originally posed to the SAB Work Group by EPA:

1. Please comment on EPA's response to the recommendations and the conclusions of the SAB (2007) Arsenic panel regarding the evaluation of the epidemiological literature.
2. Please comment on EPA's response to the SAB's recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.
3. Please comment on EPA's sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.

My comments will examine each of these original Work Group charge questions in turn.

Original Charge Question to the Work Group #1:

The SAB Work Group's analysis of the Agency's responses to the SAB (2007) Arsenic panel appears to be quite thorough. In general, the Work Group reviewed the recommendations of the 2007 SAB Panel and found EPA's responses to be generally compliant. However, there were several issues that they identified as potential weaknesses in the Agency's responses that would make for a stronger, more transparent IRIS document. These included:

Systematic literature review needs a description of criteria employed in evaluating studies.

Greater concordance between narrative description and table in Appendix B

Power calculations post hoc should not be sole descriptor of the value of epidemiological studies. Rather, relative risk point estimates and their confidence intervals should be included in these descriptions.

Discussion of studies' exposure misclassification is incomplete in the draft IRIS document. The narrative presenting these studies should provide more detailed development of the ways in which exposure misclassification can lead to under- or underestimation of risk. This discussion should be referenced and tabulated.

EPA should update their literature with studies published since 2007.

The Work Group's analysis of the EPA responses to SAB 2007 comments appears to be clear and thorough.

Original Charge Question to the work Group #2. Please comment on EPA's response to the SAB's recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.

The Work Group felt that the EPA's response to the earlier review was generally clear, but that there were specific issues that would make this a stronger IRIS document. These included:

It would be helpful if the EPA showed their results from the use of different non-linear models graphically, e.g., by showing the dose-response data and model dose-response curves for selected endpoints and age and gender classes.

The rationale from the issue paper (7/23/2005) be included in the IRIS assessment, and the reference population described in greater detail.

More detailed description of the underlying data.

Provide greater information about the variability of well water arsenic concentrations in the Taiwan studies.

Provide greater information about the sensitivity analyses. In general, it appears that the data generated by the Monte Carlo analyses are not provided in the IRIS document and renders much of this analysis difficult to interpret.

Original Charge Question to the Work Group #3. Comment on EPA's sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.

The Work Group found that the EPA's revisions were partially responsive to the recommendations of the panel. They recommend that EPA make their document more transparent the scientific basis of the exposure assumptions used and enhance the rigor and transparency of the sensitivity analysis.

The Work Group noted that much of the documentation addressing the scientific basis of the exposure assumptions is available in separate documents and that this information should be incorporated into the IRIS document. They also found that:

EPA should better explain what the analysis shows. For example, the estimate of risk was very sensitive to the non-water intake rate assumptions. Therefore, EPA should explain why this is so, and should clearly articulate the uncertainty surrounding these rate assumptions.

Better justification for default estimates. For example the default drinking water consumption rate was set at levels that were not justified in the document. The range of values employed in the sensitivity analysis should be better documented.

In addition, the Work Group finds that EPA:

Should consider additional permutations of gender-specific water consumption.

Needs to clearly delineate the basis for water concentration assumptions.

Needs to address water consumption rates of susceptible groups.

Should provide more complete and graphical analysis.

Should examine selected sets of exposure assumptions and their effect on cancer potency.

Should clarify what the exposure assumptions are intended to represent.

Should significantly strengthen the bases for the exposure assumptions selected for their Monte Carlo analysis.

Should provide a scientific explanation for limiting non-water intake to dietary sources.

Should more clearly delineate organic vs. inorganic exposure assumptions

Should provide a brief description of research gaps.

Quality Review Question #2: whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report

I found no technical errors or omissions in the report and felt that the issues were thoroughly addressed.

Quality Review Question #3: whether the Committee's report is clear and logical.

The Work Group's report was very well written and appeared to be a careful, thoughtful and thorough analysis of the EPA's responses to the earlier review. There are clear differences in the presentation of Work Group responses to the different charge questions, possibly reflecting different authors. While this document may benefit from some editorial effort to harmonize the presentation among these different charge question responses, the document is certainly a clear and sophisticated response.

Quality Review Question #4: whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

The conclusions and recommendations articulated in the Work Group's report are clear and supported by the body of the report. Very logical and constructively critical.

**Comments from Dr. Steven Heeringa (SAB Liaison: Chair, FIFRA Scientific Advisory Committee)**

EPA Science Advisory Board Quality Review  
 “Review Comments on EPA’s Responsiveness to SAB 2007 Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic”

Steven G. Heeringa,  
 November 17, 2010

The National Research Council (NRC) 1999 and 2001 committee reports and the SAB’s own 2007 report of its review of the EPA’s draft IRIS document for Inorganic Arsenic clearly identify the complexity of the problems that must be addressed in any assessment of the carcinogenicity and other toxicological risks associated with inorganic arsenic exposure. The EPA SAB’s 2007 panel report clearly acknowledged the limitations of available epidemiological studies, uncertainties over the specific mode of action for various cancer outcomes, our dependence on the Taiwanese data for dose response modeling and the model variability and uncertainty that is inherent in the choice of suitable values for many parameters related to life course exposure profiles—both for the Taiwanese population from which the data were derived and the U.S. population to which risk extrapolations must be made.

This SAB report addresses three specific charge questions from the EPA. In these three questions, the charge to the SAB panel is narrowly defined, does the revised document respond to the conclusions and recommendations of the 2007 SAB panel pertaining to:

1. Evaluation of the epidemiological literature?
2. Approach to modeling inorganic arsenic cancer risk (and the corresponding sensitivity analysis related to model form)?
3. Sensitivity analysis related to the choice of exposure inputs to the models of cancer risks?

In these charge questions, the SAB panel was not explicitly asked to comment on the Mode of Action (MOA) for multiple cancer outcomes.

Review questions:

- I. Were the original charge questions to the SAB Ad Hoc panel adequately addressed?

On the question of the EPA’s evaluation of the epidemiological literature, the draft report adequately addresses the key issues pertaining to the EPA’s evaluation of the epidemiological literature through 2007 including the importance of more carefully outlining the criteria by which the individual epidemiological studies were evaluated and a recommendation (where possible) to provide comparative quantitative summaries of the estimated relative risks and confidence intervals. In the concluding paragraph on Page 7, the report takes up the issue of whether the EPA’s review of published epidemiology studies should be censored at 2007 and takes the compromise position of suggesting that the extended literature review for 2007-2010 be folded into an addendum or appendix. While I have no strong argument against placing this updated review in an addendum, the SAB should consider the merit of recommending that the literature review for the additional years be integrated with the existing review in the body of the document that currently ends with studies published through 2007.

The report also adequately addresses the EPA Charge Question #2, covering the report's treatment of the functional form of the dose response model and the inclusion of the reference population in model fitting. The SAB report is also clear in calling for better organization and more complete detail in the EPA's description of the sensitivity analysis to improve the "transparency and scientific rationale" for the agency's model selection process. The SAB panel report uses the Charge Question 2 discussion of dose-response modeling to raise the question of MOA uncertainty for the various cancer outcomes, touch briefly on some new results in this area (page 8, lines 33-39) and then reaffirm the conclusion of previous panels that there is insufficient scientific data to support specific modes of action and therefore the EPA can be expected to default to its guidelines for linear extrapolation of the dose response curve at the very lowest levels of exposure (dose). One minor recommendation is that the SAB panel explicitly state at the end of page 8 that the linear extrapolation is an EPA guideline default that is intended to be conservative (protective) in the face of MOA uncertainty and the Panel is not endorsing this default as a "better or worse" approximation to the true cancer responses at low doses.

The 2007 SAB panel report was deliberately not prescriptive as to the exact forms of the sensitivity analyses that it recommended related to the exposure parameters in the dose-response modeling. The 2010 SAB panel concludes that the EPA's response to the 2007 call for sensitivity analyses "is adequate for meeting the minimum requirements for the intended purpose..." To its credit the 2010 SAB reports does not expand the call for additional sensitivity analysis but provides explicit and detailed guidance on how the sensitivity analysis exercise could be better designed, documented and explained to the reader.

## II. Whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report.

I identified no significant technical errors in the report. Although the report does not go into great depth in the scientific discussion or recommendations on issues (e.g. MOA) not specifically covered by the charge questions, the responses to the charge questions are technically correct. As noted above, the question remains whether the Panel's recommendation to extend review of the epidemiological studies to 2010 should be incorporated as an addendum or whether the body of the report should be updated to make this review and any cross-study comparisons or meta-analyses complete to 2010 as opposed to stopping at 2007.

On page 7, lines 12-15, the SAB panel report recommends that the EPA assessment include an expanded discussion of the estimation bias associated with model misspecification or inaccuracies in exposure estimation. This is a good recommendation but since the literature on this topic is extensive it would be good to emphasize the last sentence in that paragraph, "A simple summary could..."

## III. Whether the committee's report is clear and logical.

The committee's report is well organized in its response to the three charge questions posed by the EPA. The discussion is generally easy to follow and where it naturally becomes more complex (e.g. in the Charge question 3 critique of the sensitivity analyses) the authors have broken the discussion down into specific bullet form outline.

In the letter to the Administrator (page 2, line 21-24), the Executive Summary (page 2, Line 29-31) and the body of the report (page 10, lines 27 ff) there is a short recommendation that I found to be unclear. The wording is of the following form, "...suggests that EPA discuss how their results should be interpreted in light of existing population-level data on bladder and lung cancer risk for exposure levels that are relevant for U.S. populations." Is this recommendation hinting that the risk levels implied by the EPA's model are not realistic given empirical data on U.S. cancer rates? The body of the report goes on to discuss a "reality check". Obviously this was an important point to one or more panel members but on Page 10, lines 35-37 the report suggests maybe empirical testing of the model should be left to other "risk assessment and characterization" documents. I do not necessarily agree that some "goodness of fit" evaluation should not be included in the IRIS toxicological review. In short, I believe that this point should be clarified and if the fitted model is capable of projecting incident cases at a population level, then a comparison to real population cancer data should be appropriate for the IRIS assessment.

IV. Whether the conclusions drawn or the recommendations provided are supported by the body of the report.

With the possible exceptions noted in my responses to I through III above, I agree that the conclusions and recommendations of this report summarized in the letter to the administrator and the Executive Summary are supported in the body of the report.

**Comments from Dr. Pamela Shubat (SAB Liaison: Chair, Children's Health Protection Advisory Committee)**

Quality review questions:

1. whether the original charge questions to committees were adequately addressed:

The EPA asked three questions as a follow up to changes EPA made to the IRS Toxicological Review of Inorganic Arsenic in response to SAB recommendations (in 2007) concerning the previous draft IRIS document. The SAB Arsenic Cancer Workgroup report, Oct. 25, 2010, responded to those questions.

The first charge question was whether the 2010 draft adequately presented an evaluation of the epidemiological literature. The Workgroup found that EPA adequately identified studies published through 2007 and that the evaluation was complete although comments were offered on improvements on the presentation of the results. The Workgroup offered practical advice on presenting information on bias and confounders. The Workgroup recommended extending the literature review and evaluation beyond 2007, which seems particularly important as there are recent publications on the Taiwanese cohort and the NRC review of the epidemiological literature is recently published. EPA should be developing reference doses and drinking water health advisories and new information should be used in those analyses. However, the Workgroup might suggest that this additional effort, which in principle should continue beyond the publication date of the Toxicological Review, be presented in other documents (for example, in an IRIS literature search) as newer information may assist users in applying IRIS values in risk assessments.

The second charge question asked for comment on the EPA approach to modeling cancer risks and the sensitivity analysis for the selected model. The purpose of presenting such analysis was to better understand the robustness of the linear model in comparison to alternatives. The Workgroup commented appropriately on the underlying assumption to utilize linear low-dose extrapolation. The Workgroup found that EPA conducted the sensitivity analysis as recommended. While the Workgroup made recommendations on presenting and discussing the results in order to increase transparency of the work, the Workgroup found that EPA responded adequately to the 2007 recommendations.

The third charge question asked whether the 2010 draft adequately presented an analysis of exposure parameters used in the cancer model. The SAB found that EPA was only partially responsive to the recommendations and that a more complete response required greater transparency in the scientific justification of exposure assumptions and enhancing the rigor and transparency of the sensitivity analysis. The Workgroup described concerns in ten areas in thorough and helpful detail.

The Workgroup adequately addressed the charge question.

2. Whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the committee's report

The Workgroup limited their review to the EPA charge questions. Many additional questions seemed to have come up during the past months of review, meetings, and public testimony. The Workgroup limited the report appropriately yet included concepts that developed in discussions, such as a reality check on cancer incidence. In general, within the report the committee offered practical advice or specific recommendations following general statements such as describing a need to increase transparency.

In response to question 3, the Workgroup reviewed previous recommendations by the SAB, determined when specific recommendations had not been as thoroughly addressed as current SAB members felt was appropriate, offered very specific recommendations on the additional analysis or explanation that would clarify or complete the EPA Toxicological Review.

The question posed by EPA includes a request for comment on the exposure assumptions. Throughout the response to question 3, the Workgroup described the information that is needed to clarify the choices that EPA made in selecting exposure parameters.

I found no technical errors or omissions in those comments within my area of expertise.

3. whether the committee's report is clear and logical.

The report is well written and summarizes a great of additional scrutiny on the part of the workgroup in reviewing previous recommendations of the SAB and the current IRIS draft. The Workgroup produced a well-written, well ordered, and detailed report. I found no ambiguities.

The report is clear and logical.

4. whether the conclusions or recommendations are supported by the body of the committee's report.

In rereading the cover letter and executive summary, I find that that body of the report describes each issue thoroughly. The emphasis on certain findings may be expressed differently in the transmittal page or executive summary, but all statements are substantiated in the report.

The body of the report includes sufficient detail and discussion to support the findings of the Workgroup.

In conclusion, the SAB Workgroup expended an appropriate level of effort to conduct a careful review a controversial IRIS Toxicological Review. While the EPA's charge questions may appear to have limited the review to questions that were of greater interest to EPA than to other parties, the Workgroup did not hesitate to incorporate additional areas of interest (e.g., the interpretation of the results) in the review. The Workgroup made sensible and useful recommendations to continue the review (e.g., the literature review, an analysis of current US cancer risks) to make EPA's finding relevant to the next step of applying the Toxicological Review.

## Comments from other SAB Members

### Comments from Dr. Ingrid Burke

I carefully read the Arsenic Cancer Review Work Group Report, its summary, and the draft letter to Administrator Jackson. Arsenic toxicology is not very closely related to my expertise, though I was on the NRC Board of Environmental Science and Toxicology when at least one of those arsenic reports came out, and learned a bit at that time. Suffice it to say that my reading this time was focused on learning about the SAB review process and about cancer assessment from arsenic, as much or more than it was focused on evaluating the completeness and adequacy of the report

1. Whether the charge questions were addressed:

The charge questions were definitely answered, thoroughly, and with great care. It seems that the comments are incisive and constructive, as well as somewhat critical. While the charge questions themselves were a bit open and poorly defined (e.g. "please comment on the EPA's response..."), the report provides very good summaries of strengths, weaknesses, and recommendations for improvement. The report is quite thorough and well organized, in response to a request for comments.

2. Whether there are technical errors or omissions:

It did not appear so to me.

3. Whether the Committee's report is clear and logical, and whether conclusions follow

The report itself is very clear and logical, and the conclusions definitely follow the review structures. I have only two small suggestions. First, the executive summary would benefit from some editing that would allow the final recommendations to be more evident. For instance, for the first response, related to sensitivity analysis of the dose-response modeling, I think the text that begins with "However", should probably be bolded, or inset, and the following recommendations should be set off with bullets, and probably enumerated. This will allow a further evaluation of whether these recommendations were followed to be conducted in a very objective and easily traced way. Implementing this type of presentation that will focus the reader on where improvements can be made would improve the report as well as followups.

There are a few places where the text is hard to follow. For instance the first sentence of the 3<sup>rd</sup> paragraph on page 6 needs some editing to make sense.

There is one particular recommendation that I understand in general, but the wording leaves me wondering quite a bit about the source of the concern and the tangible recommendation. I have had to read the phrase "upper boundary ...cancer risk estimate that is of significant public concern" over and over to figure out what the authors are really saying, and I still am not sure I get it. ( I'm not a toxicologist, but I think I should be able to understand this. Is the team stating that the public would be very concerned if they knew that the cancer risk was that high, or, as I suspect, that the linear relationship makes it appear that cancer risks are so high that it could lead to more public concern than is warranted? The follow-up recommendation, that EPA discuss how risks are interpreted, is not clear to me.

## **Comments from Dr. Terry Daniel**

### **General comments**

The 2007 SAB review of the EPA IRIS assessment report on Inorganic Arsenic was thorough and constructive and focused directly on the issues the committee was charged by EPA to address. AS noted in the 2010 SAB re-review, the revised EPA report clearly and substantially responded to the recommendations of the 2007 SAB review. However, the introduction (p 31-32) to the added sections in the revised EPA report seems to isolate the SAB's suggestions rather than adopting them and incorporating them as a legitimate and valued part of the report. The new suggestions in the 10/25/2010 SAB review call for additional literature review (after 2007) and more data, descriptions and perhaps additional analyses associated with the sensitivity analysis added in response to the previous SAB review—so the issue of how to incorporate SAB advice will arise in the next draft of the EPA report. This is more a matter of style rather than substance, however, the EPA report will stand for some time as the Agency's foundation for arsenic assessments and regulations and it would be better if the report were clearly presented as an EPA consensus document, fully supported by the authors and by the SAB. Very minor editing of the cited introductory section of the EPA report (in the current 2010 draft, and/or in a draft subsequent to the current SAB-review recommendations) could avoid any appearance of dissent or resentment on the part of the authors.

The 10/25/2010 draft recommendation, responding to the 2007 revision of the EPA report suggests bringing the already substantial literature review up to date by adding references after 2007. There is a recognized danger here that the authors of the EPA report will be faced with an impossible task. Given the turnaround time between reviews, quality reviews, revisions and re-reviews, it will be very hard for the authors to keep references completely up to date. The suggestion might be more manageable if it specifically called for an appendix with a briefly annotated bibliography of major relevant literature up to 2010 (or perhaps 2011), with substantive discussion only of articles/findings that significantly affect the targeted cancer risk criteria.

### **Quality Review Questions**

1. YES: The original charge questions to SAB Ad Hoc Committee reviewing the EPA report on Arsenic Cancer risk 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. Otto Doering**

I believe that the original charge questions were met.

I do not see technical errors, but this is not my area of expertise.

The report is clear and logical.

I believe that the conclusions are supported by the text in the report.

Comment: I am interested in possibly more detail of how the review work group responded to the comments from the public in the June 16th teleconference.

**Comments from Dr. David Dzombak**

November 16, 2010

*(a) Are the original charge questions to the SAB Panel adequately addressed in the draft report?*

Each of the charge questions appears to be addressed in sufficient depth. For charge question #2, a summary statement about the adequacy of the EPA response would be helpful.

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

I did not detect any technical errors or omissions in the report, or issues that were not adequately addressed.

*(c) Is the draft report clear and logical?*

The report is well organized and easy to follow. A summary statement about the committee's view of the adequacy of the EPA response in relation to charge question #2 would be helpful, as noted above.

*(d) Are the conclusions drawn, and/or recommendations made, supported by the information in the body of the draft SAB report?*

The conclusions drawn and recommendations made are supported by information in the body of the report, with one exception. In the draft letter to the Administrator, on page 2, lines 15-17, I could not find discussion in the body of the report of the statement given there: "Providing the distribution of variability of arsenic concentrations in well water and the data and parameters used in the modeling would help to make EPA's document more transparent." Also, the relationship of this sentence to the preceding discussion in the paragraph of the letter is not very clear to me. I recommend that the sentence cited be omitted from the letter to the Administrator, or that it be modified to make more clear how it relates to the rest of the paragraph, and to material in the body of the report.

## Comments from Dr. Jeffrey Griffiths

Comments on arsenic review:

1. Whether the original charge questions were addressed:

Yes, I believe they were. The suggestions offered by the SAB report authors denote a sophisticated appreciation of the issues and controversies involved in this arena.

Multiple commentaries by the SAB members and by the public have also been provided and discuss issues which were addressed in the report. These have been carefully read, digested, and integrated into my comments. These in large part deal with the epidemiological data available; the mode of inorganic arsenic toxicity; sensitivity analysis of the dose-response relationship and modeling; and questions around exposure assessment. Issues such as exposure misclassification, temporal and spatial variability of both arsenic levels and of exposure; case and control selection; and the stability of the risk estimates were discussed. In aggregate I did not find that these areas had been neglected by the SAB working group, nor had they dismissed their importance.

While I believe that the literature published since 2007 should be analyzed, and incorporated into the EPA's risk assessment for inorganic arsenic, I do not believe it prudent to further delay the Toxicological Review of Inorganic Arsenic report until that (laborious and time consuming) task is finished, given the public health implications.

The charge questions were:

Charge Question 1: "... comment on the evaluation of the epidemiological literature." The evaluation was thorough and acknowledged the points mentioned above.

Charge Question 2: "... comment ... regarding the approach to modeling inorganic arsenic cancer risks and sensitivity analyses." This remains a topical area where there are strong passions.... and insufficient information, in my view, to justify the assumption of a non-linear dose-response relationship.

Charge Question 3: "...comment on ... sensitivity analyses and choice of exposure assumptions used for modeling cancer risk..."

I found the SAB evaluation's inclusion of a set of discrete suggestions regarding transparency of what the sensitivity analysis shows; the need for better justified default assumptions; gender-specific water consumption permutations; water concentration assumptions and water consumption rates, more graphical analysis; and exposure assumption representation to be concrete. I particularly thought the suggestion regarding layered assumptions to be valuable.

2. Were any technical errors present?

In my opinion, no.

3. Is the report clear and logical?

Yes.

4. Whether the conclusions drawn or recommendations provided, are supported by the body of the Committee's Report.

Yes, it is.

**Comments from Dr. James Hammitt**

I judge that the SAB report on organic arsenic carcinogenicity is careful, thorough, and well done. To answer the charge questions:

1. The original charge questions are well addressed.
2. I see no technical errors or omissions.
3. The report is clear and logical.
4. The conclusions and recommendations are supported.

## Comments from Dr. Bernd Kahn

Here are my comments on the 2010 Inorganic Arsenic Review:  
The Draft SAB Committee report meets the 4 quality review criteria. Please consider the following suggestions for minor changes:

Letter, p.1, 1.32: Delete 'other' after 'consider'.

1.37: Move 'more clearly' behind 'state'.

1.41: Add at end of sentence 'with brief indication concerning the implication of each on the presented Assessment'. Also on p.7, 1.33.

Letter, p.2, 1.5: Move 'linear' behind 'default'; insert comma behind 'approach'.

1.15: Delete 'distribution of'.

1.21-24: Clarify the advice about As risk discussion in other EPA documents. See also p.2, 1.29 of Executive Summary.

1.31: Replace 'has also recommended' with 'is recommending'.

p.2, 1.22: Delete 'there are' and 'that'.

p.2, 1.35 and 1.37: Change 'The 1999 NRC' to 'The NRC (1999)' or 'The 1999 NRC report'. Also 1.42 and 1.46 concerning SAB, and throughout the report, on pp. 3, 5, 9, and 11.

p.3, 1.11: Replace '; they include' with colon.

p.4, 1.4-5: This sentence does not fit here. If the committee wishes to discuss the impacts of route of exposure, chemical form, etc., it should do so in a separate paragraph, with references.

p.10, 1.42: Replace 'recommended' with 'recommend'.

**Comments from Dr. Madhu Khanna**

I have reviewed the documents you provided. I believe that the charge questions were adequately addressed and that the report is clearly and logically written and supports the conclusions reached.

**Comments from Dr. Kai Lee**

I have read the draft memorandum to Administrator Jackson regarding inorganic arsenic, and I support forwarding these comments to the Administrator.

**Comments from Dr. L.D. Mc Mullen**

I feel the Review of the Arsenic Cancer Assessment was excellent. The cover letter was just the right length and did a good job of summarizing the review. The executive summary was well written and the main document covered all the charge questions. Job well done!!!

## Comments from Dr. Judith Meyers

1. Were charge questions adequately addressed?

Yes, and I particularly valued the way the report included reference to the public comments when appropriate.

2. Are there technical errors or omissions or issues omitted?

Not my area of expertise, but I did not find any.

3. Is the report clear and logical?

Yes.

4. Are the conclusions/recommendations supported by the body of the report?

Yes.

More a question than a comment: p. 1, line 20 and p. 5, line 23 – Do you really mean ecological study? I do not know, but would think it was an epidemiological study. Perhaps this is just different jargon, but it seems like a different definition of ecology than I know (although maybe it is an ecological study, e.g. arsenic in wildlife).

p. 12, line 27 and p. 3, line 22: reference to EPA Issues Paper is pretty vague. Can you be more specific, like give the title and date? That is what was done for the one referenced earlier.

P 16, line 33: Good ending, but last phrase doesn't make sense. Do you mean "that we used 10 years ago?"

I will not be able to be on the teleconference because I will be on an airplane at that time. Based on my reading of the document and not having heard the concerns of others, I would vote that the document be approved.

**Comments from Dr. Horace Keith Moo-Young**

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;

Yes. The original charge questions to the SAB Standing Committee 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;

To my knowledge, there are no technical errors in the report.

3. whether the Committee's report is clear and logical; and

The report is logical and clearly written.

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

The conclusions drawn and recommended support the body of the report. I think that lines 31-33 on page 16 which suggests that "10 years from now, we will not find ourselves in position of relying on sparse data for risk estimate" should be reworded to state that the agency should continue to update the data set to increase the reliability and accuracy of the risk assessment. This statement seems very vague and provides the agency with no real direction.

**Comments from Dr. Amanda Rodewald**

This message includes my written comments for the SAB quality review of the SAB Report on the EPA's Responsiveness to SAB 2007 Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;

The charge questions were addressed completely and thoroughly. The organization of the responses made the report concise and clear.

2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;

I did not notice any technical errors or omissions.

As a minor comment, the use of the phrase "as medicinal uses" on lines 5-6 of page 4 was awkward (i.e., "arsenic compounds are used...as medicinal uses...").

3. whether the Committee's report is clear and logical; and

I found the report to be clear and logical.

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

The recommendations were supported within the body of the report.

### **Comments from Dr. Duncan Patten**

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

The responses appear to fully address the charge questions, but the discussion on use of linear versus non-linear models seemed a bit convoluted. Perhaps this is my lack of understanding of the direction the response was headed. Maybe that is a clarity question.

2. Any technical errors or omissions?

this is not in my field, so I really can't say.

3. Is the report clear and logical?

It appears to be, except for my slight confusion on the type of model (see response 1 above).

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

The report is very comprehensive and makes every effort to base its conclusions on literature, earlier reports, its own analyses and those of outsiders.

**Comments from Dr. Amanda Rodewald**

This message includes my written comments for the SAB quality review of the SAB Report on the EPA's Responsiveness to SAB 2007 Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;

The charge questions were addressed completely and thoroughly. The organization of the responses made the report concise and clear.

2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;

I did not notice any technical errors or omissions.

As a minor comment, the use of the phrase "as medicinal uses" on lines 5-6 of page 4 was awkward (i.e., "arsenic compounds are used...as medicinal uses...").

3. whether the Committee's report is clear and logical; and

I found the report to be clear and logical.

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

The recommendations were supported within the body of the report.

### **Comments from Dr. James Sanders**

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

Yes, the work group carefully considered and fully addressed each of the three charge questions. I found the responses to be clear and logical.

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

No, the draft report covers each of the issues.

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

Yes. I do have one minor comment. The report often refers to earlier NRC and SAB reports in what appears to be an unusual manner. For examples, please see lines 35-46 of p.2. This draft report refers to these as "The 1999 NRC noted that...". I suggest this terminology is awkward; I recommend changing these references throughout the draft report to either "The 1999 NRC report noted, or The NRC (1999) noted...".

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

Yes. Conclusions are supported by the document.

### Comments from Dr. Kathleen Segerson

- (1) The original charge questions appear to have been thoroughly addressed.
- (2) I am not in a position to judge if there are any technical errors or errors of omission.
- (3) On whether the report is clear and logical, I have only two editorial comments:

(a) There are three charge questions, corresponding to the three issues that the SAB was asked to comment on. Given this, I was expecting there to be 3 paragraphs in the letter to the administrator corresponding to these three questions. In addition, I was expecting there to be three subsections/subheadings in the executive summary corresponding to these three questions. But the paragraphs/subheadings don't map directly to the charge questions.

In the administrator's letter, it might be clearer to combine the first two paragraphs on page 2, since it appears they both relate to charge question 2. The rationale of splitting this into two paragraphs (as it is currently split) is not clear to me. If a single paragraph is too long, then it would seem to make more sense to "break" the paragraph after "relevance for this assessment." In this case, the first paragraph related to this charge question would state the SAB's support of the use of the linear default, while the second paragraph (starting with "The SAB, in 2007, also recommended...." and ending with "lung cancer incidence for the U.S. population." would focus on the sensitivity analysis part of charge question 2.

Likewise, in the executive summary, I would find it clearer if there were three subsections corresponding to the three charge questions. In the current report, both the "Mode-of-action" and "Sensitivity Analysis of Dose-Response Modeling" relate to charge question 2. I would suggest that these be included under a single subheading to make it clear that these are both part of the response to charge question 2.

(b) A minor point: In the administrator's letter, the sentence "The SAB supports its previous recommendations..." seems a little confusing. It might be clearer to state something like "The SAB continues to believe that the Taiwanese dataset is the most appropriate dataset...."

- (4) The conclusions seem well-supported.