UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

March 1, 2011

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Subject: Review Comments on EPA's Responsiveness to SAB 2007 Recommendations for the Revision of Cancer Assessment of Inorganic Arsenic

Dear Administrator Jackson:

The Science Advisory Board (SAB) received a request from the Office of Research and Development's National Center for Environmental Assessment to evaluate and comment on EPA's implementation of the SAB 2007 recommendations regarding the revision of the cancer assessment of inorganic arsenic. In response, a work group of the chartered SAB was convened to review the agency's document entitled, "*Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS),*" (EPA/635/R-10/001), focusing on three areas: evaluation of epidemiological literature, dose-response modeling approaches, and the sensitivity analysis of the exposure assumptions used in the assessment. The SAB was not asked to conduct a full peer review of the assessment, including EPA's calculation of the cancer unit risk estimate. This report has been approved by the chartered SAB.

The SAB commends the agency on its efforts to be responsive to our previous recommendations. In keeping with SAB practice, public comments were considered by the SAB during the development of this report. The SAB has made a number of recommendations to improve the clarity and transparency of the 2010 draft assessment and to strengthen the scientific basis of EPA's findings and conclusions. Key recommendations are highlighted below.

In 2007, the SAB recommended the use of the epidemiologic data on the Taiwanese population for estimating bladder and lung cancer risk in humans from exposure to inorganic arsenic. The SAB also suggested that the agency consider other epidemiologic studies from the United States and other countries, utilizing a uniform set of evaluative criteria. On the basis of available data, the Taiwanese data set remains the most appropriate data set for determining the

cancer risk from exposure to inorganic arsenic. EPA's 2010 draft assessment presents a comprehensive overview of the epidemiological literature on arsenic carcinogenicity up to 2007; however, it needs to state more clearly the set of criteria that EPA used in evaluating and presenting the studies. Where possible, the summaries of the epidemiology studies should include a quantitative or qualitative presentation of the relative risk point estimates and the associated confidence intervals. Additionally, EPA should consider including an addendum or appendix describing major epidemiology studies that were published since 2007 and that could substantially impact the calculated cancer unit risk estimate.

In 2007, the SAB noted that there was a possibility of a nonlinear dose-response at low exposures to arsenic, but due to the lack of a complete understanding of the mode-of-action by which inorganic arsenic causes cancer in humans, the choice of a specific nonlinear model could not be justified. The SAB supports the agency's choice of using a default linear approach given the complexity of the mode-of-action of arsenic. Although extensive new research has been done in this area, there is not enough information in the literature to fully define the multiple modes-of-action for arsenic carcinogenicity.

The SAB, in 2007, also recommended that EPA consider using alternative dose-response models and perform a sensitivity analysis of the Taiwanese data with different exposure metrics. EPA's 2010 draft assessment uses a default linear low-dose extrapolation and evaluates the differences between a linear model and three non-linear models: quadratic, quadratic exponential and linear exponential. The SAB finds that, while the sensitivity analysis did respond to the 2007 recommendation, a more detailed description of the data sets used in the risk model is needed. 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. The SAB notes that, while EPA's choice of a linear approach is consistent with EPA's risk assessment default procedures, it has produced a calculated upper-bound cancer risk estimate for arsenic that is of significant public health concern. The SAB suggests that EPA discuss, possibly in other EPA complete risk assessment documents, how the estimated risks for arsenic should be interpreted in light of current estimated bladder and lung cancer incidence for the U.S. population.

In 2007, the SAB recommended that the agency conduct sensitivity analyses to determine the potential impact of different choices of exposure assumptions (both water and non-water consumption) for estimating arsenic cancer potency. The SAB finds that the agency was partially responsive to the previous recommendations. The SAB recommends that the agency revise its assessment to provide a more detailed and transparent explanation of the scientific rationale for its choice and use of alternative exposure assumptions. The SAB has also recommended ways to enhance the rigor and transparency of the sensitivity analysis for the exposure assessment through further documentation, explanation and analyses.

The SAB appreciates the opportunity to provide advice on EPA's inorganic arsenic cancer assessment. We look forward to the upcoming review of the IRIS assessment of non-cancer effects from arsenic exposure. The SAB underscores the importance of developing

integrated, interdisciplinary IRIS assessments and is amenable to conducting a future review of a synthesized assessment of arsenic health effects, as needed.

Sincerely,

/signed/

Dr. Deborah L. Swackhamer, Chair
EPA Science Advisory Board

/signed/

Dr. Elaine Faustman, Chair
SAB Arsenic Cancer Workgroup

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EXECUTIVE SUMMARY

Various committees have evaluated the assessment of cancer risk associated with exposure to inorganic arsenic. They include two National Research Council (NRC) committees (1999, 2001) and the EPA Science Advisory Board (SAB) in 2007. In 2010, EPA's National Center of Environment Assessment (NCEA) within the Office of Research and Development (ORD) requested the SAB evaluate and comment on the agency's implementation of the SAB recommendations in 2007 regarding EPA's revision of the cancer assessment of inorganic arsenic. In response, a workgroup of the chartered Board reviewed EPA's draft document entitled, "*Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)*," (EPA/635/R-10/001) and was asked to comment on three areas: evaluation of epidemiological literature; dose-response modeling approaches; and the sensitivity analysis of the exposure assumptions used in the risk assessment. The SAB was not asked to conduct a full peer review of the assessment, including EPA's calculation of the cancer risk estimate. A summary of the SAB responses to EPA's charge questions follows with further details included in the body of the report.

Evaluation of epidemiological data

The NRC in 1999 and 2001 concluded that ecological studies from the arsenic endemic area of Taiwan provide the best available empirical human data and are appropriate for use in dose-response assessment of arsenic in drinking water. In 2007, the SAB also supported the use of the epidemiologic data on the Taiwanese population for estimating human cancer risk for inorganic arsenic, especially to identify the potential range of responses of human populations.

The SAB agrees with these previous findings and the draft 2010 assessment that, based on the current data, the Taiwanese data set remains the most appropriate data set for determining the population risk of cancer from exposure to inorganic arsenic. The SAB also notes that the EPA's draft 2010 assessment includes a comprehensive listing of the epidemiological literature on arsenic and cancer up to 2007; however, the set of criteria that were used in evaluating the studies needs to be better presented. The SAB recommends that, where possible, the summaries of the epidemiology studies should include a quantitative or qualitative presentation of the relative risk point estimates for a specific exposure comparison and the associated confidence intervals. Furthermore, the SAB suggests that EPA consider including an addendum or appendix describing major epidemiology studies published since 2007 that could substantially impact the calculated cancer risk estimate.

Mode-of-action and sensitivity analysis of dose-response modeling

The NRC in 1999 and 2001 concluded that the available mode-of-action data on arsenic did not provide a biological basis for using either a linear or nonlinear extrapolation. In 2007, the SAB concluded that inorganic arsenic has the potential for a highly complex mode-of-action and until more was learned about the complex pharmacokinetic and pharmacodynamic properties of

inorganic arsenic and its metabolites, there was insufficient justification for the choice of a specific nonlinear form of the dose-response relationship.

The SAB concludes that there are multiple potential mechanisms for arsenic carcinogenicity and potential target tissues. The SAB notes that although a large amount of research is available on arsenic's mode-of-action, the exact nature of the carcinogenic action of arsenic is not yet clear. Therefore, there is not enough information in the literature to define a mode-of-action for all of the relevant cancer endpoints for this assessment. The SAB recommends that this complexity and limited understanding of the mode-of-action of arsenic should be openly acknowledged in the 2010 draft assessment.

In 2007, the SAB recommended that EPA consider using alternative dose-response models and perform a sensitivity analysis of the Taiwanese data with different exposure metrics, with the subgroup of villages with more than one well measurement and using a multiplicative model that includes a quadratic term for dose. The SAB finds that the sensitivity analysis of dose-response modeling presented in the 2010 draft assessment was responsive to the SAB previous recommendations. The SAB agrees with the conclusion that none of the alternative models (i.e., quadratic, quadratic exponential and linear exponential) evaluated by EPA materially changed the estimated risk levels versus use of a linear model. EPA also evaluated whether the models were inordinately affected by the high end of the dose-response curve and found that they were not. However, the SAB believes that more transparency and a better scientific rationale for the agency's selection process are needed. To improve the clarity and transparency of the draft assessment, a number of aspects of the sensitivity analysis should be described in greater detail. They include the need for a more detailed description of the Taiwanese data sets used in developing the risk model; a better description of the distribution of well water arsenic concentrations across and within the 42 exposed villages; and a further explanation of the sensitivity displayed for female bladder cancer risks. The SAB notes that, while EPA's choice of a linear approach is consistent with EPA's risk assessment procedures, it has produced a calculated upper-bound cancer risk estimate for arsenic that is of significant public health concern. The SAB suggests that EPA discuss, possibly in other EPA complete risk assessment documents, how the estimated risks for arsenic should be interpreted in light of current estimated bladder and lung cancer incidence for the U.S. population.

Exposure assessment and sensitivity analysis

The 1999 NRC report noted that the assessment of arsenic exposure via drinking water is often based on the measurements of arsenic concentrations in drinking water and assumptions regarding the amount of water consumed. The 2001 NRC report added that the method used to characterize arsenic dose in a study is a source of uncertainty in arsenic dose-response assessment. Furthermore, the NRC report noted that the choice of the dose measurement affects the interpretation of an epidemiological study and the choice of the dose-response model. The 2007 SAB agreed that water consumption (via drinking water, in beverages, or in cooking water) assumptions could have an impact on the assessment of arsenic's risk. However, the 2007 SAB did not recommend specific values for EPA to use in evaluating dose-response in the Taiwanese study nor for levels of exposure in the U.S. population risk estimates. It instead recommended

that uncertainty in exposure parameters be evaluated for both the Taiwanese study population and the U.S. populations through sensitivity analyses. The 2007 SAB recommended that EPA evaluate the drinking water consumption rate assumptions used with regard to highly exposed and sensitive subpopulations. Additionally, the NRC (2001) recommended that EPA consider the background dietary intake of inorganic arsenic and incorporate the adjustment values. The 2007 SAB also concluded that arsenic levels in food are important considerations for EPA's assessment of lung and bladder cancer risk associated with exposures to arsenic in drinking water. The 2007 SAB stated that a range of total arsenic food intake values should be included in the sensitivity analyses.

The SAB finds EPA's revisions to the IRIS assessment to be partially responsive to SAB's 2007 recommendations regarding the exposure assumptions. The SAB provides two primary general suggestions for improving the responsiveness of the assessment; they include, making more transparent the scientific basis of the exposure assumptions used; and enhancing the rigor and transparency of the sensitivity analysis. The basic approach to the sensitivity analysis is adequate for meeting the minimum requirements for the intended purpose, and is responsive to the SAB recommendation in that the impact of choice of assumptions is shown in terms of specific cancer risks (lung and bladder, males and females). There are sufficient data to support development of variability and/or uncertainty distributions for some inputs, such as drinking water consumption rates in the United States, but the data are not available to assign corresponding distributions for the Taiwanese populations.

The SAB notes that much of the documentation addressing the scientific basis of the exposure assumptions is available through separate documents (e.g. EPA Issues Paper, 2005d) that, if incorporated within the agency's draft IRIS assessment, will help address the SAB's concerns. The SAB recommends that relevant information from these documents be integrated within the current document as appropriate with the goal of enhancing transparency and scientific credibility. The SAB has provided specific suggestions, within the body of the report, for making the scientific basis of the exposure assumptions used more transparent and for enhancing the rigor, and transparency, of the sensitivity analyses.

BACKGROUND

Arsenic is a naturally occurring element that is found throughout the environment. Exposure to inorganic arsenic can result in different health outcomes depending upon the route of exposure. Arsenic compounds are used as a mordant in the textile industry, for preserving hides, as medicinals, pesticides, pigments, and wood preservatives. EPA's health effects assessment for inorganic arsenic was first made available on the Integrated Risk Information System (IRIS) database in 1988. Various committees have reviewed aspects of the EPA's revised assessment of cancer risk associated with exposure to inorganic arsenic. They include two National Research Council (NRC) committees (1999, 2001) that concluded that the cancer risk for inorganic arsenic should be based on internal cancers (lung and bladder) instead of skin cancers. In 2005, the SAB was asked to review several EPA documents including:

- Office of Pesticide Programs' (OPP) *Draft Science Issue Paper: Mode-of-action for Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation* (U.S. EPA OPP, 2005a)
- Office of Research and Development (ORD) Issue Paper *Cancer Risk Assessment for Organic Arsenical Herbicides: Comments on Mode of Action, Human Relevance and Implications for Quantitative Dose-Response Assessment* (Appendix E of U.S. EPA OPP, 2005, USEPA ORD, 2005b).
- Office of Water's (OW) Draft *Toxicologic Review of Inorganic Arsenic* (U.S. EPA OW, 2005c).

At that time, the SAB convened a panel of experts to provide advice on the metabolism, mode of action, dose-response, and approaches to low-dose extrapolation of cancer risk for Dimethylarsinic Acid (DMA^{v}) and inorganic arsenic (iAs). The SAB review report (EPA-SAB-07-008) was issued in June 2007 and is available at http://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/EADABBF40DED2A0885257308006741EF/$File/sab-07-008.pdf.

In 2010, ORD's National Center for Environmental Assessment (NCEA) requested the SAB evaluate and comment on EPA's implementation of SAB (2007) key recommendations in the 2010 draft assessment entitled, "*Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS),*" (EPA/635/R-10/001). In response to this request, the SAB convened a workgroup of the chartered Board to comment on the agency's charge questions that focused on three areas: evaluation of epidemiological literature, dose-response modeling approaches, and the sensitivity analysis of the exposure assumptions used in the risk assessment. The SAB was not asked to conduct a full peer review of the assessment, including EPA's calculation of the cancer risk estimate. The SAB workgroup held a public face-to-face meeting, on April 6-7, 2010, to discuss and deliberate on its responses to EPA's charge questions. The chartered Board conducted a quality review of the work group's draft report (May 13, 2010) at a public teleconference on June 16, 2010 and a revised draft was again reviewed on November 22, 2010. The final SAB report incorporates the SAB quality review comments and public comments, both written and oral, which were received throughout the advisory process.

RESPONSES TO EPA'S CHARGE QUESTIONS

Charge Question 1:

The SAB concluded that the Taiwanese data set (Wu 1989; Chen et al., 1988, 1992) remains the most appropriate data set to determine carcinogenic risk due to exposure to iAs. They recommended that EPA should evaluate other published epidemiology studies using a uniform set of criteria and document these findings in the assessment. They also stated that if one or more studies provide potential utility, comparisons should be provided in the assessment.

EPA agreed that the Taiwanese data were the best available for determining the carcinogenic risk due to exposure to iAs. In response to SAB's recommendation, an extensive review and evaluation of all available human studies for iAs using the criteria suggested by the SAB was performed by EPA and is summarized in Section 4.1 of the draft IRIS assessment and included in tabular format in Appendix B. EPA concluded in the 2010 draft IRIS assessment that there were no additional epidemiological studies that had comparable utility to the Taiwanese data set (Wu 1989; Chen et al., 1988, 1992).

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.

Response:

In 1999, the NRC concluded that ecological studies from the arsenic endemic area of Taiwan provide the best available empirical human data for assessing the risks of arsenic-induced cancer. The 2001 NRC report also concluded that the data from southwestern Taiwan remain appropriate for use in dose-response assessment of arsenic in drinking water. In 2007, the SAB supported the use of the epidemiologic data on the Taiwanese population for estimating human cancer risk for inorganic arsenic especially to identify the potential range of responses of human populations. The 2007 SAB urged the agency to consider other epidemiologic studies from the United States and other countries, utilizing a uniform set of evaluative criteria, as they develop their risk assessment. The 2007 SAB recommended consideration of the following additional factors when reviewing the studies:

1. Estimates of the level of exposure misclassification;
2. Temporal variability in assigning past arsenic levels from recent measurements;
3. The extent of reliance on imputed exposure levels;
4. The number of persons exposed at various estimated levels of waterborne arsenic;
5. Study response/participation rates;
6. Estimates of exposure variability;
7. Control selection methods in case-control studies; and
8. The resulting influence of these factors on the magnitude and statistical stability of risk estimates.

The SAB concludes that EPA has been responsive to the 2007 SAB recommendations in evaluating the epidemiology studies published through 2007. The 2010 draft IRIS assessment presents a well organized and very comprehensive overview of the epidemiological literature on arsenic and cancer through 2007. The SAB recognizes that there are limitations that are inherent in the design of environmental epidemiological investigations, particularly regarding reconstruction of past exposure levels. EPA has described the limitations of each study in Section 4.1 of the draft IRIS assessment, and presented a summary of study strengths and limitations in the tables of Appendix B. The systematic review of the literature, however, needs to more clearly state the set of criteria that were used in evaluating the studies. Additional clarification and documentation on how various study design factors were considered and weighted in the evaluation are needed. In addition, there are aspects of studies that are discussed in Section 4.1 narrative that are not included in the summary table of Appendix B. The SAB recommends that the tables in Appendix B be reformatted to present the study summaries more clearly and in a more consistent format including adding any essential information from references into the text for clarity.

The SAB supports the 2007 SAB conclusion that the Taiwanese data set (Wu 1989; Chen et al., 1988, 1992) remains the most appropriate data set for determining the population risk of cancer to exposure to inorganic arsenic. The limitations of the Taiwanese studies are well presented, particularly regarding the ecologic study design, use of death certificates, and assumptions regarding lifetime individual arsenic exposure. The strengths of these studies include availability of community drinking water exposure levels, large populations and person-years of follow-up, and consideration of important potential confounders including socioeconomic status, lifestyle, dietary patterns, and medical care. The SAB acknowledges the concerns expressed regarding the limitations of the Taiwanese data set; however given the fundamental mission of EPA to protect public health, these well conducted and extensively reviewed studies remain the most appropriate critical studies.

The SAB received public comments that suggested when comparing the large number of epidemiological studies that demonstrate varying results the power calculations for the studies can provide important insights and should be taken into consideration. The power of an epidemiological study is the probability of detecting an association of a specified strength between exposure and disease if one exists. For example, in studies where statistical significance is not achieved, failure to identify an association may be a reflection of a limitation of the power of the study. The SAB, however, notes that while the relative power of various studies is important to convey, this should not be done by presenting only power calculations. Power calculations are useful in planning a study, but after the study is completed, the most informative presentation of epidemiologic findings that combines both the observed results and reflects the power of the study is the relative risk (RR) point estimates for a specified exposure comparison and the associated confidence intervals. Furthermore, systematic presentation of numbers of individuals in each exposure stratum provides the reader with a sense of relevant sample size within strata and the robustness of the exposure contrast. While a restricted range of exposure within a study population will limit estimation, it is also likely that studies carried out at a lower-level of exposure will be estimating an effect smaller than that at higher levels for a categorical comparison of higher-exposed to lower-exposed. For instance, the required sample size should be larger when a smaller range of exposures is observed (e.g., the U.S. studies), since the expected magnitude of the RR for low-level exposure is lower. The SAB also recognizes that many published arsenic studies may not present

specific power calculations or RR and that a detailed quantitative comparison is difficult. Where possible, the summaries of the epidemiology studies should include a quantitative or qualitative presentation of the relative risk point estimates for a specific exposure comparison and the associated confidence intervals. This should be included both in the study descriptions in Section 4.1 and in the table of studies in Appendix B.

As noted by public comments, the SAB agrees that failure to control potential confounders or misclassification of study population exposure levels may bias study results. In the presentation of one of the critical epidemiology studies (Chen et al. 1992), the IRIS assessment (p.38) states, "a weakness of the study is the assumption that an individual's arsenic intake remained constant from birth to the end of the follow-up period; this flaw possibly led to the underestimation of risk." Other epidemiological studies also had similar issues. Indirect measures of individual exposure were used to estimate population exposure levels for all of the epidemiology studies. In Section 4.1, the narrative presenting the epidemiology studies should include a more detailed discussion of bias including literature citations addressing the potential for bias, both underestimating and overestimating of risk, due to confounders or limitations in exposure estimation. While the existence of bias can usually be proposed with some certainty, the key issue is whether the quantitative consequences of bias are of sufficient magnitude to be of concern. Methods are available for this purpose (see, for example: Lash, Fox, and Fink: *Applying Quantitative Bias Analysis to Epidemiological Data*, Springer, 2009). The SAB suggests that the IRIS assessment include a simple table that identifies potential biases (misclassification of exposure, misclassification of disease, omitting potential confounders, etc.) and the potential magnitude and direction of bias in inferences that are drawn from the study data. A simple summary could then relate these sources of bias to their impact in the data and methods used in the IRIS assessment.

The IRIS 2010 assessment includes an extensive review of published epidemiology studies up to and including the year 2007. The SAB recognizes that the assessment cannot be continually updated with every newly published paper and it is not the purpose of IRIS to provide real time summaries of advancing science. However, given the large amount of ongoing research on the health effects of arsenic, the SAB has concerns about the 2007 cutoff. In order to ascertain if new studies will impact the 2010 assessment, 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 assessment due to large sample size or effect estimate that is substantially different from that estimated by Chen et al. (1988, 1992).

Charge Question 2:

The SAB noted the possibility of a nonlinear dose-response at low exposures, but due to uncertainty in the mode-of-action (including pharmacokinetics and dynamics) the use of a linear low dose extrapolation approach to determine the cancer risk for iAs was recommended using cancer incidence from the Taiwanese data set. In addition, the SAB stated that EPA should perform a sensitivity analysis for the variables in the cancer modeling with respect to the Taiwanese data set (i.e., exposure metrics, subgroup of villages with more than one well measurement, and a multiplicative model that includes a quadratic term for dose). The SAB

concluded that overall, EPA had implemented the recommended modeling by NRC (2001). Also, the SAB made recommendations to perform a sensitivity analysis regarding the robustness of the model and alternative formulations.

Consistent with the SAB recommendations, EPA used a linear low-dose extrapolation approach and conducted a sensitivity analysis of nonlinear forms of the dose-response in the 2010 draft IRIS assessment. EPA also explored nonlinear forms of the dose-response from the Taiwanese data set (Wu 1989; Chen et al., 1988, 1992). Sensitivity analyses using alternative dose-response models produced potency estimates similar to the linear approach.

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.

Response:

Mode-of-action and dose-response modeling

The 1999 NRC Committee concluded that the mechanism or mode-of-action by which inorganic arsenic causes toxicity, including cancer, is not well established. This conclusion was again supported by the NRC in 2001 which noted that although a large amount of research is available on arsenic's mode-of-action, the exact nature of the carcinogenic action of arsenic is not yet clear. Therefore, the 2001 NRC report concluded that the available mode-of-action data on arsenic did not provide a biological basis for using either a linear or nonlinear extrapolation.

In 2007, the SAB concluded that inorganic arsenic has the potential for a highly complex mode-of-action and until more is learned about the complex pharmacokinetic and pharmacodynamic properties of inorganic arsenic and its metabolites, there is not sufficient justification for the choice of a specific nonlinear form of the dose-response relationship. The NRC (2001) concluded that the most appropriate approach was to base risk assessments on a linear dose response model that includes the Southwestern Taiwan population as a comparison group.

The SAB agrees that there are multiple potential mechanisms for arsenic carcinogenicity and potential target tissues which make it very difficult to do a single risk assessment model. This complexity and limited understanding of the mode-of-action of arsenic should be openly acknowledged in the 2010 draft IRIS assessment. While there is an ever increasing literature on arsenic, there is not enough information in the literature to define a mode-of-action for all of the relevant cancer endpoints for this assessment. The SAB notes that it is a reasonable hypothesis that bladder cancer is the result of repeated cell injury, cell death and compensatory proliferation; but there is not enough specific data at this point to confirm the hypothesis, nor are there hypotheses to explain the role of arsenic in lung cancer. For these reasons, the SAB concurs with EPA's rationale for choosing a linear default approach for risk assessment.

Sensitivity Analysis

The 2007 SAB recommended that EPA perform a sensitivity analysis of the Taiwanese data with different exposure metrics, with the subgroup of villages with more than one well measurement and using a multiplicative model that includes a quadratic term for dose. The SAB finds that the sensitivity analysis of dose-response modeling presented in the 2010 IRIS assessment was responsive to the previous 2007 SAB recommendations. Specifically, EPA was asked to evaluate a model using a quadratic term for dose. EPA evaluated the differences between a linear model and three non-linear models: quadratic, quadratic exponential and linear exponential. Results are described on p. 143, which concludes that "within the range of exposures covered by the epidemiological data, the alternative forms predict very similar risks." It would be very helpful if the results could be shown graphically, e.g., by showing the dose-response data and model dose-response curves for selected endpoints and age and gender classes. The SAB agrees with the conclusion that none of the alternative models materially changed the estimated risk levels versus use of a linear model. EPA also evaluated whether the models were inordinately affected by the high end of the dose-response curve. They were not. This was evaluated by running the models without the highest exposure group. EPA evaluated whether exclusion of a reference population influenced the dose-response curve. Results of this analysis (see Fig. 5-2) suggest that exclusion of the reference population did have an effect on risk estimates. EPA evaluated the pros and cons of including a comparison population in a 2005 issues paper (Issue Paper: Inorganic Arsenic Cancer Slope Factor, Final Draft, July 23, 2005). The SAB recommends that the rationale from the issue paper be included in the draft IRIS assessment, and the reference population described in greater detail. This will provide more transparency and strengthen the scientific rationale for the agency's selection process.

To improve the clarity and transparency of the draft IRIS assessment, there are a number of aspects of the sensitivity analysis that should be described in greater detail. They include:

- **More detailed description of underlying data.** The assessment would benefit from a more detailed description of the Taiwanese data sets used in developing the risk model. The data sets are briefly described in section 4.1.1 as part of the review of the Chen et al. 1988a, 1992 and Wu et al., 1989 studies, and key features are summarized in Table B-1. However, readers are required to piece together this information on their own in order to understand the basis for the risk modeling presented in section 5.3.

- **Variability of well water arsenic concentrations.** The distribution of well water arsenic concentrations across and within the 42 exposed villages is not adequately described. Only medians and ranges across the whole set of villages are presented in Table B-1. While the assessment mentions that the number ranged from 2 – 47 measurements, the variability of measurements both within and across wells within a given village is not provided. This information needs to be presented to assist in understanding the results of the sensitivity analysis the 2007 SAB requested. It would also be helpful to see a more quantitative characterization of how the 1974-1976 well water re-testing results differed from the results of tests conducted in 1962-1964, on which the risk modeling relied. Table B-1 indicates the results were "similar"; however, it is not clear how to interpret this.

- **Upper and lower limits in water concentration.** EPA responded to SAB's request for sensitivity analysis or Monte Carlo analysis with respect to well water concentrations in the villages with more than a single measurement by re-estimating the model using minimum and maximum values of the concentrations for each village. Table 5-10 indicates the effect (in terms of estimated cancer incidence) is up to about a ± 30% change. Although EPA used upper and lower limits, rather than low and high percentile values or Monte Carlo analysis as SAB had suggested, the sensitivity analysis responds adequately to the recommendation. As noted above, however, more information on the variability in the underlying water concentration data is needed to substantiate the reported models and results.

- **Modeling data and parameters.** The SAB suggests that EPA publish the data and parameter tables used in its modeling analysis. As requested by the 2007 SAB report, this would strengthen the scientific credibility and transparency in the assessment.

- **Selection of a reference population.** EPA has tested the sensitivity of the risk model with respect to the choice of reference population (southwest Taiwan, all Taiwan, or no reference population) and to the value of non-water arsenic intake (i.e., in accordance with EPA's document, this refers to food intake) for both reference and exposed populations. Results indicate that the cancer incidence risks are fairly robust, with the exception of female bladder cancer risks. The sensitivity displayed for female bladder cancer risks seems to warrant further explanation – the result is described, but not explained, in the accompanying text (pp. 141-2). Additionally, EPA should examine whether any combinations of these parameter variations will affect the assessment– e.g., using different non-water intake values in combination with a different reference population.

The SAB notes that there is tremendous interest in the risk associated with consumption of water that is contaminated with inorganic arsenic and 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. The idea of providing a "reality check" on the estimated risk levels was discussed. The SAB recognizes that IRIS toxicological reviews are not intended to provide a complete risk assessment but rather a summary and synthesis of the toxicological evidence that supports risk assessment. Hence, an estimation of risk attributable to arsenic in drinking water in U.S. populations versus the observed incidence of cancer is not appropriate within the purview of this document. The SAB considers this as a difficult but important exercise and recognizes that this is probably better suited for inclusion in other risk assessment and characterization documents developed by the agency.

Charge Question 3:

The SAB did not recommend specific values for the exposure assumptions or parameters used in the cancer model. They did, however, recommend evaluating the impact on the cancer

risk of using a range of values, assessing the variability, and conducting a sensitivity analysis for exposure parameters (e.g., water intake, background dietary exposure).

EPA evaluated the impact on the estimated cancer risk of using a range of exposure parameter values (e.g., water intake, background dietary exposure), assessed variability, and conducted a sensitivity analysis. After the completion of these analyses, values were chosen for exposure assumptions based upon the best available science taking into account the NRC (2001) recommendations.

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.

Response:

The 1999 NRC report noted that assessment of arsenic exposure via drinking water is often based on the measurements of arsenic concentrations in drinking water and assumptions regarding the amount of water consumed. Such data are estimates, the uncertainty of which will depend on the method used. The 2001 NRC report added that the method used to characterize arsenic dose in a study is a source of uncertainty in arsenic dose-response assessment. Furthermore, the NRC report noted that the choice of the dose measurement affects the interpretation of an epidemiological study and the choice of the dose-response model.

The 2007 SAB agreed that water consumption (via drinking as water, in beverages, or in cooking water) assumptions have a substantial impact on the assessment of arsenic's risk. However, the 2007 SAB did not recommend specific values for EPA to use in evaluating dose-response in the Taiwanese study nor for levels of exposure in the U.S. population risk estimates. It did recommend that uncertainty in this parameter be evaluated for both the Taiwanese study population and the U.S. populations at risk. The 2007 SAB recommended that EPA should:

1) Evaluate the impact of drinking water consumption rates associated with more highly exposed population groups with differing exposures and susceptibilities (e.g., children, pregnant women);
2) Incorporate variability parameters for individual water consumption into their analysis for dose-response in the Taiwanese population as they have done for the U.S. population;
3) Conduct sensitivity analyses of the impact of using a range of consumption values for the Taiwanese population;
4) Provide a better justification for assuming different consumption levels by gender or in the absence of such a justification, conduct additional sensitivity analyses to examine the impact of equalizing the gender-specific consumption level;
5) More fully articulate and document how different sources of water intake, as well as variability, are incorporated into the risk model (e.g. data for intake from beverages and cooking water).

The NRC (2001) recommended that EPA consider the background dietary intake of inorganic arsenic and incorporate the adjustment values of 0, 10, 30, and 50 μg per day into the

cancer risk calculations. The 2007 SAB also agreed that arsenic levels in food are important considerations for EPA's assessment of lung and bladder cancer risk associated with exposures to arsenic in drinking water. However, the 2007 SAB once again did not recommend a specific value for EPA to use in its base risk assessment. It did recommend a range of values for consideration by EPA in its sensitivity analysis and the 2007 SAB offered suggestions to EPA for additional analytical steps to clarify the impact of food levels of arsenic on dose-response and exposure as it revises its risk estimates. The 2007 SAB recommended that EPA should:

1) Conduct sensitivity analyses using a range of total arsenic food intake values from at least 50 to 100 μg per day to perhaps as high as 200 μg per day to assess the impact of this range of dietary intakes on risk of lung and bladder cancer from exposure *via* drinking water in the Taiwan cohort;
2) Not assume that the control population has an intake value of zero arsenic from food;
3) Apply greater rigor in their discussions of data used in these assessments (e.g., sources, methodological and analytical issues, bioavailability); and
4) Give immediate research attention to the issue of arsenic bioavailability.

The SAB finds EPA's revisions to the IRIS assessment to be partially responsive to the 2007 SAB recommendations regarding the sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk. The SAB provides two primary general suggestions for improving the responsiveness of the assessment. They include, making more transparent the scientific basis of the exposure assumptions used and enhancing the rigor and transparency of the sensitivity analysis.

The basic approach to the sensitivity analysis is adequate for meeting the minimum requirements for the intended purpose, and is responsive to the 2007 SAB recommendation in that the impact of choice of assumptions is shown in terms of specific cancer risks (lung and bladder, males and females). In evaluating the consequences of choices regarding modeling assumptions and intake values, the IRIS assessment states, "The agency felt that the currently available data were insufficient to support detailed probabilistic uncertainty and variability estimation." The SAB agrees with this conclusion. There are sufficient data to support development of variability and/or uncertainty distributions for some inputs, such as drinking water consumption rates in the United States, but the data are not available to assign corresponding distributions for the Taiwanese populations.

The SAB notes that much of the documentation addressing the scientific basis of the exposure assumptions was available through separate documents (e.g. EPA Issues Paper, 2005d) that if incorporated within the current assessment, will help address the SAB's concerns. The SAB recommends that relevant information from these documents be integrated within the current document as appropriate with the goal of enhancing transparency and scientific credibility.

The SAB is providing the following specific suggestions for making the scientific basis of the exposure assumptions used more transparent and enhancing the rigor and transparency of the sensitivity analysis.

- **Better explanation of what the sensitivity analysis shows.** The sensitivity analyses presented offer insight as to how the cancer potency estimates change as drinking water consumption and non-water arsenic intake assumptions change. The various non-water arsenic intake rate assumptions produced modest changes in risk, with the exception of bladder cancer risk in females. This calculated risk was very sensitive to the non-water intake rate assumption. The assessment and this analysis will be strengthened by providing a short explanation for why this is the case.

- **Need for better justified default assumptions.** Despite some effort to discuss drinking water consumption rates and sources of information for non-water arsenic intake rates, the reasons for some of the specific values chosen to be included in the sensitivity analyses are not clearly justified. For example, the "default" drinking water consumption rate for Taiwanese males is 3.5 L/day, citing precedent from U.S. EPA (1988), Chen et al. (1992), and NRC (1999 and 2001). For the sensitivity analysis, alternative values of 2.75, 3.0, and 5.1 L/day were evaluated [along with alternative values for Taiwanese females]. No rationale is provided for these specific numbers, other than they are thought by the agency to span a "reasonable range of values" (see page A-6). To enhance transparency in this example, it would be helpful to know the scientific basis for selecting the lowest and highest numbers (defining the range). Also, if the intent was to illustrate effects at the boundaries of the range of drinking water consumption rates, it is unclear why the lowest estimate for males (2.75 L/day) was not consistent with the lowest estimate for females (2.0 L/day) (see Table 5-10), especially given the SAB's request to justify different consumption values for men and women. Furthermore, no values for drinking water consumption rates for Taiwanese women were evaluated below the "default" rate of 2.0 L/day, suggesting that the value selected by the agency is at the limit of the range of reasonable values for this parameter. The effects on risk were determined based on assumptions that both the reference and exposed populations had non-water intake rates of 0, 30, and 50 µg/day arsenic. Although compliant with SAB's 2007 recommendations, better discussion of dietary intake of inorganic arsenic would help the reader understand whether the various values included in the analysis represent different interpretations of the existing data, bounding estimates, or something else.

- **Consider additional permutations of gender-specific water consumption.** The 2007 SAB recommended: "Because data on gender differences in consumption in Taiwan are limited, a better justification for assuming different consumption levels by gender is needed, particularly given the lack of sex difference in consumption in United States and observed in studies from other countries (Watanabe et al., 2004). In the absence of such a justification, the SAB recommends an additional sensitivity analysis to examine the impact of equalizing the gender-specific consumption level." The agency complied with this recommendation to some extent, evaluating the effect on risk of setting the drinking water consumption rate for both Taiwanese males and females at 2.75 L/day in the sensitivity analysis. However, the basis for the choice of this particular drinking water consumption rate is not explained. Also, by examining a single drinking water consumption rate for both sexes, the influence of selection of different rates on resulting risk is not illustrated. In order to be responsive to the 2007 SAB recommendation,

discussion of the impact of using a single drinking water consumption rate for males and females for the Taiwanese populations needs to be justified and expanded.

- **Need to clearly delineate the basis for water concentration assumptions.** Based on the data in tables 5-10 and 5-11, it isn't clear if EPA has completed the calculations that the SAB requested. Those tables noted that the sensitivity analyses used minimum and maximum village water arsenic concentration values. It isn't clear if only the villages with more than one well measurement were used or if all the villages were used. EPA needs to clarify the water concentration assumptions. This recommendation is also consistent with recommendations under charge question #2.

- **Need to address water consumption rates of susceptible groups.** The 2007 SAB recommended that the "EPA should evaluate the impact of drinking water consumption rates associated with more highly exposed population groups with potentially different exposures and susceptibilities (e.g. children, pregnant women) in its arsenic exposure estimates as the agency determines the overall effects of drinking water consumption rates on arsenic risk." In the current 2010 draft IRIS assessment, the impact of drinking water consumption rates associated with more highly exposed population groups with potentially different exposures and susceptibilities (e.g. children, pregnant women) in its arsenic exposure estimates has not been evaluated. During the April meeting, the agency indicated that including these populations in the sensitivity analysis would be difficult and of limited value. So that the response to this 2007 SAB comment is clear, an explanation of why this aspect of the sensitivity analysis was not conducted should be included in Appendix A.

- **More complete and graphical analysis.** EPA has responded to the 2007 SAB's suggested sensitivity analysis with the development of Tables 5-10 and 5-11 along with Figure 5-2 showing the influence of various exposure assumptions including water arsenic concentration, non-water arsenic intake, and water consumption on various cancer endpoint risks. The tables and figure are efficient in providing a "snapshot" of their influence for various assumed point estimates; however, a more complete description of their influence can be shown by graphing across the range of plausible values. Admittedly, the graphical representation will be less efficient (i.e., require more space) but will provide a more complete depiction. To the extent possible, it would be useful to illustrate on these graphs the various historically and currently "assumed" values.

- **Testing the effects of layered assumptions.** To further respond to the 2007 SAB's recommendation, EPA tested the effects of changing assumptions one at a time. This approach is necessary to clearly show how individual values potentially affect cancer potency and risk. This approach does not, however, indicate how changes in assumptions might interact to produce overall changes in potency and risk. Testing all of the various permutations of changes in assumptions in a sensitivity analysis would be arduous and of dubious value. Nevertheless, it may be instructive to examine selected sets of exposure assumptions and their effect on cancer potency. This would provide an indication of the extent to which a reasonable range of exposure assumptions in the aggregate has the potential to affect cancer potency estimation.

- **Clarification of what the exposure assumptions are intended to represent.** It is often unclear in the assessment whether the exposure assumptions (e.g., drinking water consumption rate) selected are intended to represent best estimates of the mean for the exposed population, upper confidence estimates of the mean, upper percentile values, upper confidence limit estimates of an upper percentile value, or something else. This should be specified in the IRIS assessment. During the April meeting, the agency indicated that different types of assumptions may be appropriate for different values. The rationale for why a particular value is used should be provided in the IRIS assessment. For example, why an upper percentile drinking water ingestion rate is appropriate for the U.S. population, while an average (or upper bound average) assumption is used for the Taiwanese population.

- **The bases for the exposure assumptions selected are not adequately described.** The SAB in 2007 stated, "Much greater rigor needs to be applied in discussing and presenting documented data sources and making clear the basis on which assumptions are being made and the relative strength of those assumptions." That criticism applies to the 2010 version of the IRIS assessment as well. Some examples include:

    - For non-water arsenic intake, EPA has selected an assumed intake value of 10 μg/day. Discussion in support of this selection occurs on pgs. 123-124 of the revised assessment and is based on six references including US EPA (1989), Schoof et al. (1998), Yost et al. (1998), NRC (1999), NRC (2001), and EPA (2005c). Of these, there are only two references that relate to the peer-reviewed primary literature, reflecting the scarcity of data from which to base this estimate. Although EPA does a reasonable job of discussing these reports, the current assessment lacks a specific rationale or justification for the selected value. It appears that the US EPA 1989 reference supporting an intake range of 2 μg/day to 16 μg/day may provide the rationale for this selection. Since this reference is not easily available, the SAB recommends that within the IRIS assessment a more complete discussion of data and evidence supporting this intake range be provided in a manner similar to what has been provided for Schoof et al. 1998 and Yost et al. 1998. In the current assessment, it is unclear what the 2 to 16 μg/day estimate is based on. Moreover, the current assessment does not provide a specific justification or rationale for this selection, but rather makes a broad statement "Based on available information, EPA selected 10 μg /day as the best estimate for non-water arsenic intake (food sources) in baseline calculations." The selection of this value can be strengthened by: 1) elaborating on the lack of data or evidence upon which to base this estimate; 2) distinguishing between evidence that is primary (i.e., peer-reviewed with data collection) and reports that provide expert assessment, and 3) providing specific and scientific justification for the selected value that can be traced to the primary literature. Again, because of the effect this parameter has on the risk estimates, providing support for the values chosen for this parameter is important.

    - The current dose-response assessment is based on an assumed water intake value of 3.5 and 2.0 L/day for men and women, respectively. As with the assumed values for

non-water intake above, justification for these values can be strengthened by establishing a clear link to data within the primary literature where possible. The specific relevant findings from Chen et al. 1992 and Chowdhury et al. 2001 should be provided in relation to the selected values. In the current assessment, it appears that EPA justified the selected values largely based on precedent (e.g., EPA and NRC reports) rather than on the data reported in the primary literature. It is unclear why EPA did not base their estimate on the data of Chowdhury et al. 2001 since it is unique and relevant. No discussion is provided of the data available from Chen et al. 1992. To the extent that EPA relies on previous EPA and NRC assessments, the link to the primary data (if available) should be maintained. The problem illustrated by the 2010 assessment is that these assumed values take on a life of their own and the evidence upon which they are based is lost, i.e., the scientific basis for the assumptions is no longer discernible.

- **The reason for limiting non-water intake to dietary sources is not explained.** Non-water exposure is currently assumed to consist entirely of arsenic in the diet. For completeness and transparency, EPA should provide a short description of alternate routes of exposure (e.g. inhalation, non-dietary ingestion, dermal absorption) from other media such as soil and include arsenic intake estimates using EPA's routine exposure assumptions for both the Taiwan and the U.S. populations; EPA should provide justification for why these other exposures were not considered in the current dose-response assessment. If the reason is that other pathways are assumed to be minor relative to arsenic intake from diet, some illustration of this should be provided as justification.

Other Comments

- **More clear delineation of organic vs. inorganic exposure assumptions.** It would be helpful to provide a paragraph for IRIS users explaining why the organic arsenic compounds do not affect the risk estimates for inorganic arsenic. The explanation will probably be fairly straight forward for the seafood organic arsenic compounds. This may not be as straight forward for any organic arsenic compound in produce (e.g. rice, etc.). As a related comment, when discussing non-water arsenic intake care should be taken to distinguish between inorganic and organic or total arsenic in food. The current draft assessment is in some places ambiguous, referring simply to “arsenic.” (see pages 123-124).

- **Value in identifying research gaps.** Given the importance and scarcity of data for purposes of estimating exposure, the SAB suggests that EPA provide a short paragraph describing the research needs along with suggested designs to produce credible estimates for water and non-water intake rates. The research needs are not only to provide point estimates, but data for distribution analysis to support the more credible stochastic approaches to risk estimation. Maybe 10 years from now, we will not find ourselves in the position that we are in now of relying on largely the same sparse/inadequate data for risk estimation that we were in 10 years ago.

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APPENDIX A - Minor edits

- Pages 139 and 140: Providing some information in these tables about the range in village water arsenic concentrations would be useful.
- Type in footnote for Table 5-11. Table 5-8 should probably be Table 5-10.
- Page 141, line 27. Tables 5-6 and 5-9 should be Tables 5-10 and 5-11
- Page 142 – line 3. Should both increased and decreased be there?