

SAB 05/13/2010 Draft

DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

[DATE]

EPA-SAB-10-xxx

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

Subject: Review of Agency's interpretation and implementation of the key SAB (2007) recommendations in the revised draft assessment "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)" (EPA/635/R-10/001).

Dear Administrator Jackson:

In 2005, the SAB was asked to review several documents that were developed by the Agency based on new information that had been generated on the metabolism, pharmacokinetics (PK), mode of carcinogenic action of arsenic and health effects of arsenic generated since the publication of reviews by the National Research Council (NRC, 1999, 2001). EPA considered this new science in the development of the Office of Pesticide Programs' (OPP) *Draft Science Issue Paper: Mode of Action for Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation* (USEPA OPP, 2005) and the Office of Water's (OW) *Draft Toxicologic Review of Inorganic Arsenic* (USEPA OW, 2005). EPA's Office of Research and Development (ORD) further captured key scientific issues to be considered in its 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 USEPA OPP, 2005, USEPA ORD, 2005). The SAB convened a panel of experts to offer advice on the metabolism, mode of action, dose-response, and approaches to low-dose extrapolation of cancer risk for Dimethylarsinic Acid (DMA) and inorganic arsenic (iAs). The SAB review was completed and the final report was transmitted to EPA in June 2007.

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

EPA ORD's National Center for Environmental Assessment (NCEA) has now developed a draft 2010 IRIS assessment "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)" (EPA/635/R-10/001). This draft assessment includes an evaluation and characterization of the potential cancer hazard of inorganic arsenic and a quantitative dose-response cancer assessment for iAs. The draft assessment also provides responses to SAB's previous review comments and recommendations. NCEA has now asked the SAB to focus their review and comments on EPA's interpretation and implementation of the key 2007 SAB recommendations in three areas: evaluation of epidemiological literature; dose-response modeling approaches; and the sensitivity analysis of the exposure assumptions used in the risk assessment.

In response to EPA's request, the SAB convened a workgroup of the chartered Science Advisory Board (SAB), the Inorganic Arsenic Cancer Review Work Group (the "work group"). The work group deliberated on the Agency's charge questions during an April 6-7, 2010 face-to-face meeting. [The final draft of the work group's report was then reviewed and approved during a meeting of the chartered SAB on XXXXXXXX.]

The SAB appreciates the Agency's effort to be responsive to the SAB 2007 recommendations. While EPA's assessment has satisfactorily addressed the issues and suggested analyses proposed by the 2007 SAB review, the SAB work group has provided a number of recommendations to improve the transparency and clarity of the conclusions that were presented. Specifically, the SAB recommends that, as the EPA proceeds with its revisions of the 2010 draft IRIS assessment, more detailed information be included within the IRIS document to make it stand-alone without the need to refer to numerous other documents such the NRC 2001 report and other internal Agency documents. It is especially important that this IRIS assessment explain the rationale for critical choices in EPA's cancer risk calculations, and not simply cite earlier reports to provide this information. A more detailed description of these recommendations is contained in the body of the report.

The SAB appreciates the opportunity to provide EPA with advice on this important subject. We look forward to receiving the Agency's response.

Sincerely,

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

Dr. Elaine M. Faustman, Chair
SAB Inorganic Arsenic Cancer
Review Work Group

SAB 05/13/2010 Draft

DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to the problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. Reports of the EPA Science Advisory Board are posted on the EPA website at <http://www.epa.gov/sab>.

**U.S. Environmental Protection Agency
Chartered Science Advisory Board
SAB Work Group for the Arsenic Cancer Review**

CHAIR

Dr. Elaine Faustman, Professor, Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington, Seattle, WA

SAB MEMBERS

Dr. Timothy Buckley, Associate Professor and Chair, Division of Environmental Health Sciences, College of Public Health, The Ohio State University, Columbus, OH

Dr. Thomas Burke, Professor, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Dr. Deborah Cory-Slechta, Professor, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Dr. George Daston, Victor Mills Society Research Fellow, Product Safety and Regulatory Affairs, Procter & Gamble, Cincinnati, OH

Dr. Agnes Kane, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

Dr. Nancy K. Kim, Senior Executive, New York State Department of Health, Troy, NY

Dr. Jana Milford, Professor, Department of Mechanical Engineering, University of Colorado, Boulder, CO

Dr. Eileen Murphy, Manager, Division of Water Supply, New Jersey Department of Environmental Protection, Trenton, NJ

Dr. Stephen M. Roberts, Professor, Department of Physiological Sciences, Director, Center for Environmental and Human Toxicology, University of Florida, Gainesville, FL

SCIENCE ADVISORY BOARD STAFF

Dr. Sue Shallal, Designated Federal Officer, U.S. Environmental Protection Agency, Science Advisory Board Staff Office, Washington, DC

**U.S. Environmental Protection Agency
Science Advisory Board
BOARD**

CHAIR

Dr. Deborah L. Swackhamer, Professor and Charles M. Denny, Jr., Chair in Science, Technology and Public Policy and Co-Director of the Water Resources Center, Hubert H. Humphrey Institute of Public Affairs, University of Minnesota, St. Paul, MN

SAB MEMBERS

Dr. David T. Allen, Professor, Department of Chemical Engineering, University of Texas, Austin, TX

Dr. Claudia Benitez-Nelson, Associate Professor, Department of Earth and Ocean Sciences and Marine Science Program, University of South Carolina, Columbia, SC

Dr. Timothy Buckley, Associate Professor and Chair, Division of Environmental Health Sciences, College of Public Health, The Ohio State University, Columbus, OH

Dr. Thomas Burke, Professor, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Dr. Deborah Cory-Slechta, Professor, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Dr. Terry Daniel, Professor of Psychology and Natural Resources, Department of Psychology, School of Natural Resources, University of Arizona, Tucson, AZ

Dr. George Daston, Victor Mills Society Research Fellow, Product Safety and Regulatory Affairs, Procter & Gamble, Cincinnati, OH

Dr. Costel Denson, Managing Member, Costech Technologies, LLC, Newark, DE

Dr. Otto C. Doering III, Professor, Department of Agricultural Economics, Purdue University, W. Lafayette, IN

Dr. David A. Dzombak, Walter J. Blenko Sr. Professor of Environmental Engineering, Department of Civil and Environmental Engineering, College of Engineering, Carnegie Mellon University, Pittsburgh, PA

Dr. T. Taylor Eighmy, Vice President for Research, Office of the Vice President for

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

Research, Texas Tech University, Lubbock, TX

Dr. Elaine Faustman, Professor, Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. John P. Giesy, Professor and Canada Research Chair, Veterinary Biomedical Sciences and Toxicology Centre, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Dr. Jeffrey Griffiths, Associate Professor, Department of Public Health and Community Medicine, School of Medicine, Tufts University, Boston, MA

Dr. James K. Hammitt, Professor, Center for Risk Analysis, Harvard University, Boston, MA

Also Member: COUNCIL

Dr. Rogene Henderson, Senior Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

Dr. Bernd Kahn, Professor Emeritus and Associate Director, Environmental Radiation Center, School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA

Dr. Agnes Kane, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

Dr. Nancy K. Kim, Senior Executive, New York State Department of Health, Troy, NY

Dr. Catherine Kling, Professor, Department of Economics, Iowa State University, Ames, IA

Dr. Kai Lee, Program Officer, Conservation and Science Program, David & Lucile Packard Foundation, Los Altos, CA

Dr. Cecil Lue-Hing, President, Cecil Lue-Hing & Assoc. Inc., Burr Ridge, IL

Dr. Floyd Malveaux, Executive Director, Merck Childhood Asthma Network, Inc., Washington, DC

Dr. Lee D. McMullen, Water Resources Practice Leader, Snyder & Associates, Inc., Ankeny, IA

Dr. Judith L. Meyer, Distinguished Research Professor Emeritus, Odum School of Ecology, University of Georgia, Lopez Island, WA

Dr. Jana Milford, Professor, Department of Mechanical Engineering, University of Colorado, Boulder, CO

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

Dr. Christine Moe, Eugene J. Gangarosa Professor, Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA

Dr. Eileen Murphy, Manager, Division of Water Supply, New Jersey Department of Environmental Protection, Trenton, NJ

Dr. Duncan Patten, Research Professor, Hydroecology Research Program, Department of Land Resources and Environmental Sciences, Montana State University, Bozeman, MT

Dr. Stephen Polasky, Fesler-Lampert Professor of Ecological/Environmental Economics, Department of Applied Economics, University of Minnesota, St. Paul, MN

Dr. Stephen M. Roberts, Professor, Department of Physiological Sciences, Director, Center for Environmental and Human Toxicology, University of Florida, Gainesville, FL

Dr. Amanda Rodewald, Associate Professor, School of Environment and Natural Resources, The Ohio State University, Columbus, OH

Dr. Joan B. Rose, Professor and Homer Nowlin Chair for Water Research, Department of Fisheries and Wildlife, Michigan State University, East Lansing, MI

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, University of Southern California, Los Angeles, CA
Also Member: CASAC

Dr. James Sanders, Director and Professor, Skidaway Institute of Oceanography, Savannah, GA

Dr. Jerald Schnoor, Allen S. Henry Chair Professor, Department of Civil and Environmental Engineering, Co-Director, Center for Global and Regional Environmental Research, University of Iowa, Iowa City, IA

Dr. Kathleen Segerson, Professor, Department of Economics, University of Connecticut, Storrs, CT

Dr. V. Kerry Smith, W.P. Carey Professor of Economics, Department of Economics, W.P. Carey School of Business, Arizona State University, Tempe, AZ

Dr. Herman Taylor, Director, Principal Investigator, Jackson Heart Study, Jackson, MS

Dr. Barton H. (Buzz) Thompson, Jr., Robert E. Paradise Professor of Natural Resources Law at the Stanford Law School and Perry L. McCarty Director, Woods Institute for the Environment, Stanford University, Stanford, CA

Dr. Paige Tolbert, Professor and Chair, Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA

SAB 05/13/2010 Draft

DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

Dr. Thomas S. Wallsten, Professor and Chair, Department of Psychology, University of Maryland, College Park, MD

Dr. Robert Watts, Professor of Mechanical Engineering Emeritus, Tulane University, Annapolis, MD

SCIENCE ADVISORY BOARD STAFF

Dr. Angela Nugent, Designated Federal Officer, 1200 Pennsylvania Avenue, NW 1400F, Washington, DC, Phone: 202-343-9981, Fax: 202-233-0643, (nugent.angela@epa.gov)

SAB 05/13/2010 Draft

DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

**SAB's Review Comments on EPA's draft Toxicological Review of
Inorganic Arsenic: In Support of the Summary Information on the
Integrated Risk Information System (IRIS)**

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

BACKGROUND

The SAB received a request from the EPA's Administrator to evaluate and comment on the Agency's interpretation and implementation of the key SAB (2007) recommendations in the revised draft assessment "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)" (EPA/635/R-10/001). This draft assessment includes a revised evaluation and characterization of the potential cancer hazard of inorganic arsenic (iAs) and a revised quantitative dose-response cancer assessment for iAs. The draft assessment also provides a response to the SAB's review comments and recommendations on the previous draft from 2005, provided to EPA in 2007. EPA is seeking to obtain a focused review of their responses to several key 2007 SAB recommendations in the 2010 revised draft IRIS assessment.

In response to this request, the SAB convened a workgroup of the chartered Science Advisory Board (SAB), the Inorganic Arsenic Cancer Review Work Group (the "Work Group"), to deliberate on the Agency's specific charge questions during an April 6-7, 2010 face-to-face meeting. The charge questions 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 (see Attachment A).

The current IRIS assessment for inorganic arsenic (iAs) was posted on the Integrated Risk Information System (IRIS) database twenty-two years ago in 1988. In 2003, the U.S. Environmental Protection Agency (EPA) decided to update the 1988 IRIS assessment to address recommendations made by a National Research Council (NRC 2001) panel that concluded that the cancer risk for iAs should be based on internal cancers (lung and bladder) instead of skin cancers. The EPA evaluated and implemented the NRC (2001) recommendations and in 2005 submitted a draft Toxicological Review of Inorganic Arsenic (or IRIS assessment) to the EPA's SAB for external peer review. The SAB review was completed and the final report was submitted to the EPA Administrator in June 2007 (see EPA-SAB-07-008 at www.epa.gov/sab). EPA revised its IRIS assessment based on the SAB 2007 recommendations.

The 2010 draft IRIS assessment and its references provide an overview of the sources of exposure to iAs, reviews the epidemiological and toxicological data for iAs and its metabolites, characterizes the hazard posed by iAs exposure for carcinogenic health effects based on the available scientific evidence, evaluates the utility of the available epidemiological studies for assessing cancer risk, includes the derivation of an oral slope factor for carcinogenic effects, and contains a series of sensitivity analyses of assumptions and alternatives in the risk assessment modeling. The assessment contains a description and analysis of studies published up to 2007. A summary of the SAB (2007) recommendations and EPA's response is provided in Appendix A of the 2010 draft IRIS assessment. This assessment does not derive non-cancer human health toxicity values (e.g., chronic reference dose, RfD) for inorganic arsenic. The non-cancer IRIS assessment is currently under development and has not yet been released for public comment or external peer review.

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

RESPONSES TO THE CHARGE QUESTIONS

Charge Question 1:

The SAB concluded that the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992) remains the most appropriate dataset 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 dataset (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:

The selection of critical studies for determination of carcinogenic risk

The work group agrees with the 2007 SAB finding and the IRIS 2010 document that the Taiwanese dataset (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 work group reviewed the complete summary of available studies and evaluated the extensive public comments provided. The limitations of the studies are well presented, particularly regarding the ecologic study design, use of death certificates, and assumptions regarding lifetime individual arsenic exposure. The strengths of the studies include well categorized 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. Given the fundamental mission of EPA to protect public health, these well conducted and extensively reviewed studies remain the most appropriate critical studies.

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

Review and evaluation of available human studies

The work group finds that EPA has been responsive to the 2007 SAB recommendations. The 2010 draft IRIS report presents a well organized and very comprehensive overview of the epidemiological literature on arsenic and cancer. More specifically, the 2007 SAB recommended consideration of the following issues when reviewing the studies.

1. Estimates of the level of exposure misclassification.
2. Temporal variability in assigning past arsenic levels from recent measurements.
3. Extent of reliance on imputed exposure levels.
4. 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.
8. Resulting influence of these factors on magnitude and statistical stability of cancer risk estimates.

The IRIS 2010 document is responsive to these issues. The work group recognizes that there are limitations that are inherent in the design of environmental epidemiological investigations, particularly regarding reconstruction of past exposure levels. However, EPA has done a thorough job of describing limitations of each study in section 4.1 of the document, and in presenting a summary of both strengths and limitations in the tables of appendix B.

Evaluation of other published epidemiology studies using a uniform set of criteria

The work group feels that EPA has been responsive to the SAB recommendations in evaluating the published epidemiology studies. The description of the review includes the criteria used in evaluating each of the studies. However, during the discussions there was some concern over presentation format and content. . Additional clarification and documentation on how various study design factors were considered and weighted in the evaluation is needed. In addition, there are aspects of studies that are discussed in the part 4.1 narrative that are not included in the summary table of Appendix B.

Recommendation:

The systematic review of the literature needs to more clearly state the set of criteria that were used in evaluating the studies. In addition, the work group recommends that the table of studies (Appendix B) be reformatted to present the study summaries more clearly and in a more consistent format including pulling any essential information from references into text for clarity.

Presentation of the power of the studies

The power of an epidemiology study is the probability of detecting an association between exposure and disease if one exists. When comparing a large number of studies that demonstrate varying results, the power calculations for the studies can provide important insights. For example, in negative studies, failure to identify an association may be a reflection of a limitation of the power of the study. The work group recognizes that many published arsenic studies may not present specific power calculations and that a detailed quantitative comparison is difficult.

Recommendation:

Where possible, the summaries of the epidemiology studies should include a quantitative presentation or discussion of the relative power. This should be included both in the study descriptions in part 4.1 and in the table of studies in Appendix B.

Bias toward the null due to study limitations regarding exposure and confounders

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 document (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 lead to the underestimation of risk.” Indirect measures of individual exposure were used to estimate population exposure levels for all of the epidemiology studies.

Recommendation:

In part 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 underestimation and overestimation of risk, due to confounders or limitations in exposure estimation.

Consideration of epidemiology studies published after 2007

The IRIS 2010 document includes an extensive review of published epidemiology studies up to and including the year 2007. The work group recognizes that the document 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 work group had some concerns about the 2007 cutoff.

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

Recommendation:

In order to ascertain if new studies will impact the 2010 assessment, EPA should consider including an addendum or appendix summarizing major epidemiology studies published since 2007.

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 dataset. In addition, the SAB stated that EPA should perform a sensitivity analysis for the variables in the cancer modeling with respect to the Taiwanese dataset (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 dataset (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:

Determining the responsiveness of the sensitivity analysis

The sensitivity analysis of dose-response modeling was responsive to the previous SAB review. Specifically, EPA was asked to evaluate a model using a quadratic term for dose. They 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

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

shown graphically, e.g., by showing the dose-response data and model dose-response curves for selected endpoints and age and gender classes. The work group agrees with the conclusion that none of the alternative models materially changed the estimated risk levels versus use of a linear model. The 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 rationale from the issue paper should be included in the IRIS review, and the reference population described in greater detail.

The need for additional details to explain the sensitivity analysis

There are a number of aspects of the sensitivity analysis that should be described in greater detail.

Recommendations:

- **More detailed description of underlying data.** The report would benefit from a more detailed description of the Taiwanese datasets used in developing the risk model. The datasets 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 report mentions that the number ranged from 2 – 47 measurements, the variability of measurements 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 1962-64, 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

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

village. Table 5-10 indicates the effect (in terms of estimated cancer incidence) is up to about a $\pm 30\%$ 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 work group suggests that EPA publish the data and parameter tables used in its modeling analysis. As requested by the 2007 SAB report, this would assist with transparency in the assessment.
- **Selection of a reference population.** EPA has tested the sensitivity of the risk model to the choice of reference population (southwest Taiwan, all Taiwan, or no reference population) and to the value of non-water arsenic 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 might consider whether any combinations of these parameter variations should be examined – e.g., using different non-water intake values in combination with a different reference population.

Mode of Action and linear vs. non linear approaches

The work group noted that there is an ever increasing literature on arsenic, however there is not enough information in the literature to definitively describe a mode of action for the cancer endpoints of relevance for this evaluation. The work group 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 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 work group concurred with EPA's rationale for choosing a linear approach for risk assessment

Recommendation:

Based on currently available information the work group accepted EPA's choice to keep a linear approach for their risk assessment

Explanation of the risk calculation

The idea of providing a "reality check" on the estimated risk levels was discussed. The calculated risk levels in the IRIS document are higher than what is normally encountered in cancer risk assessments for environmental contaminants. This may cause confusion for

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

individuals who have high levels of exposure. For clarity it is important that EPA emphasize that their estimates are based on upper 95th percentile of possible risk values.

Recommendation:

Because there is tremendous interest in the iAs water contamination, the work group suggests that EPA discuss how the results should be interpreted in light of existing population-level data on bladder and lung cancer risk for US-relevant exposure levels. Since IRIS toxicological reviews are not intended to be a full risk assessment and an estimation of attributable risk due to drinking water arsenic may not be appropriate, this discussion is probably better suited for inclusion in other risk assessment and characterization documents developed by the Agency.

Charge 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:

In the context of this charge question, the work group found EPA's revisions to the subject document to be partially responsive to SAB's 2007 review. The work group has two primary general suggestions:

- 1) make more transparent the scientific basis of the exposure assumptions used; and
- 2) enhance the rigor and transparency of the sensitivity analysis.

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

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). In evaluating the consequences of choices regarding modeling assumptions and intake values, the review states, “The Agency felt that the currently available data were insufficient to support detailed probabilistic uncertainty and variability estimation.” This is reasonable. There are sufficient data to support development of variability and/or uncertainty distributions for some inputs, such as drinking water consumption rates in the U.S., but trying to assign corresponding distributions for the Taiwanese populations would be largely guesswork.

Recommendations:

- **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 document and this analysis will be strengthened by providing a short explanation 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 cryptic. 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). For the sake of transparency in this example, it would be helpful to know if the lowest and highest number (defining the range) are entirely arbitrary or if there is a scientific basis for their selection. 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 combined 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. Also, no values for drinking water consumption rate 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 if both the reference and exposed populations were assumed to have non-water intake rates of 0, 30, and 50 µg/day arsenic. Although compliant with SAB recommendations, better discussion of dietary intake of inorganic arsenic would help the reader

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

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.** SAB (2007) 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 U.S. and observed in studies from other countries (Watanabe et al., 2004). In the absence of such a justification, the work group 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 testing only one equal-gender drinking water consumption rate, 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 equalizing gender-specific drinking water consumption rates for the Taiwanese populations on risk estimates needs to be 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.
- **Need to address water consumption rates of susceptible groups.** The 2007 SAB Panel 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.” This issue is not addressed in the current toxicological review. 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 SAB’s suggested sensitivity analysis with the development of Tables 5-10 and 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

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy

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.** Testing the effects of changing assumptions one at a time is necessary to clearly show how individual values potentially affect cancer potency at 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.

Exposure Assumptions

The work group noted that during our face-to-face meeting with EPA, much of the documentation addressing the scientific basis of the exposure assumptions was provided through separate documents (e.g. EPA Issues Paper) that if incorporated within the current document, will help address the work group’s concerns. The work group recommended that these documents be added and connection to address the following points be added.

Recommendations:

- **Clarification of what the exposure assumptions are intended to represent.** It is often unclear in the document 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 review. During the April meeting, the Agency indicated that different types of assumptions may be appropriate for different values. That may be the case, but the rationale for each value needs to be provided in the review; 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 review as well. Some examples include:

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

- For nonwater arsenic intake, EPA has landed on an assumed intake value of 10 µg/day. Discussion in support of this selection occurs on pg 123-4 of the revised document 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 report lacks a specific rationale or justification for the selected value. It appears that the US EPA 1989 reference supporting an intake range of 2 to 16 µg/day held sway in this selection. Since this reference is not easily available, it is recommended that within the current document a more complete discussion of data and evidence supporting this intake range is provided in a manner similar to what has been provided for Schoof et al. 1998 and Yost et al. 1998. In the current document, it is unclear what the 2 to 16 µg/day estimate is based on. Moreover, the current document 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 nonwater 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 nonwater 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 report, it appears that EPA selected values largely justified 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 relevant and some of the only data available. 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 current document is that these assumed values take on a life of their own and we lose track of the evidence upon which they are based.

SAB 05/13/2010 Draft
DO NOT CITE OR QUOTE

This draft SAB panel report has been prepared for quality review and approval of the chartered SAB.
This report does not represent EPA policy

- **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 US populations; EPA should provide justification for why these other exposures were not considered in the current dose-response assessment. Presumably, the reason is that other pathways are assumed to be minor relative to arsenic intake from diet, but some illustration of this should be provided in order to be convincing that this is in fact the case.

Additional Comment

- **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, discussion of non-water arsenic intake should be careful to distinguish between inorganic and organic or total arsenic in food. The current draft is in some places ambiguous, referring simply to “arsenic.” (see pages 123-124).

Minor comments

- Pages 139 and 140: Would providing some information in these tables about the range in village water arsenic concentrations 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?

General Comment (outside the IRIS process)

- **Value in identifying research gaps.** Given the importance and scarcity of these data for purposes of estimating risk, it is suggested that EPA provide a short paragraph describing the research needs along with suggested designs to produce credible estimates for water and nonwater 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 10 years ago.

**NCEA's Proposed Charge to External Reviewers for the
IRIS Toxicological Review of Inorganic Arsenic (cancer)
February, 2010**

Introduction

The current IRIS assessment for inorganic arsenic (iAs) was posted on the Integrated Risk Information System (IRIS) database in 1988. In 2003, the U.S. Environmental Protection Agency (EPA) decided to update the 1988 IRIS assessment to address recommendations made by a National Research Council (NRC 2001) panel which concluded that the cancer risk for iAs should be based on internal cancers (lung and bladder) instead of skin cancers. The EPA evaluated and implemented the NRC (2001) recommendations and in 2005 submitted a draft Toxicological Review of Inorganic Arsenic (or IRIS assessment) to the EPA's Science Advisory Board (SAB) for external peer review. The SAB review was completed and the final report was submitted to the EPA Administrator in June 2007 (see EPA-SAB-07-008 at www.epa.gov/sab). EPA now seeks to obtain a focused SAB review of the responses to several key SAB (2007) recommendations in the 2010 revised draft IRIS assessment. The assessment will appear on the Agency's online IRIS database when completed.

The 2010 draft IRIS assessment provides an overview of the sources of exposure to iAs, reviews the epidemiological and toxicological data for iAs and its metabolites, characterizes the hazard posed by iAs exposure for carcinogenic health effects based on the available scientific evidence, evaluates the utility of the available epidemiological studies for assessing cancer risk, includes the derivation of an oral slope factor for carcinogenic effects, and contains a series of sensitivity analyses of assumptions and alternatives in the risk assessment modeling. A summary of the SAB (2007) recommendations and EPA's response is provided in Appendix A of the 2010 draft IRIS assessment. This assessment does not derive noncancer human health toxicity values (e.g., chronic reference dose, RfD) for inorganic arsenic. The noncancer IRIS assessment is currently under development and has not yet been released for public comment or external peer review.

Charge Overview

The goal of this focused external peer review is to evaluate EPA's implementation of the key SAB (2007) external peer review recommendations. This focused review should concentrate on EPA's responses to the SAB comments in Appendix A and the corresponding revisions in the 2010 draft IRIS assessment. Please provide specific responses to the Charge below. If there are recommendations for further changes or additions to the assessment, please provide specific information on how those changes could be implemented with the currently available scientific information.

Please note, each of the following Charge questions is preceded by a brief overview of the recommendations and conclusions provided to the EPA by the SAB in their final report to the Administrator as well as an overview of EPA's response. This text is to provide context to the Charge that focuses on the key recommendations and conclusions made by the SAB. The complete SAB (2007) document is found at www.epa.gov/sab (EPA-SAB-07-008). Please refer to Appendix A of the 2010 draft IRIS assessment for EPA's response.

Charge to the SAB Arsenic Review Panel

Charge 1:

The SAB concluded that the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992) remains the most appropriate dataset 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 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 dataset (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.

Charge 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 dataset. In addition, the SAB stated that EPA should perform a sensitivity analysis for the variables in the cancer modeling with respect to the Taiwanese dataset (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 dataset (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.

Charge 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.