United States Environmental Protection Agency

Inorganic Arsenic IRIS Assessment (Cancer)

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United States Environmental Protection Agency

Purpose

The goal of this focused external peer review is to evaluate EPA's implementation of key SAB (2007) external peer review recommendations regarding the draft IRIS Toxicological Review for Inorganic Arsenic (cancer).

Time Course for Inorganic Arsenic Assessment

CANCER ASSESSMENT

2003	IRIS Assessment initiated
2005	Submitted to SAB (July)
	SAB Arsenic review Panel Public Teleconference (Aug)
	SAB Arsenic review Panel Public Face-to-Face meeting (Sept)
2006	SAB Arsenic Review Public Teleconference (Jan)
	SAB Arsenic Review Public Teleconference (Feb)
	SAB Arsenic Review Public Teleconference (Feb)
	SAB Chartered Board Teleconference (Nov)
2007	SAB completes review
2008	EPA completes revisions based on SAB 2007 review
	Submitted to Agency Review and Interagency Review (Oct)
2009	Resubmitted to Interagency Review
2010	Submitted to 2nd SAB

Public Comments & External Peer Review

6 Opportunities for public comments since 2005

- **Oral and written comments provided to the panel**

2 External peer reviews

- **2007 Science Advisory Board External Peer Review**
  - 2 years to complete (2005-2007)
- **2010 Science Advisory Board External Peer Review**

2007 External Peer Review

- SAB Peer Review Panel reviewed an issue paper on dimethylarsinic acid (DMA) and the 2005 Draft Toxicological Review of Inorganic Arsenic
- Diverse SAB panel (21 panel members)
- 12 total charge questions, 6 charge questions on iAs seeking input on qualitative and quantitative aspects of draft assessment:
  - Mode of Action (B3)
  - Choice of principal study (C2)
  - Low-dose extrapolation (D2)
  - Cancer Modeling (D3)
  - Modeling Assumptions (D4, D5)
- Appendix A of the 2010 Draft Toxicological Review summarizes the 2007 SAB conclusions and recommendations, and EPA's implementation of revisions

Derivation of the Oral Cancer Slope Factor

- National Research Council (NRC) 1999 set the stage for assessing cancer risk on internal cancers (bladder and / or lung) versus skin cancers.
- For the derivation of the oral Cancer Slope Factor (CSF), EPA implemented the approach recommended by the NRC 2001.
- Public comments were considered by the 2007 SAB Panel and EPA.
- Considered and implemented 2007 SAB conclusions and recommendations.
  - Evaluated epidemiological studies
  - Evaluated MOA Information for supporting the cancer assessment
  - Followed the study selection and dose response model recommendations
  - Corrected model errors
  - Explained the exposure assumptions used to generate cancer risk estimates
  - Conducted sensitivity analyses
- Comparison of the oral CSF in the 2005 Draft to the 2010 Draft Toxicological Review of inorganic arsenic yields an approximate 4.5 fold increase

Summary

- The current draft of the Inorganic Arsenic assessment has been underway since 2003; the SAB reviewed the 2005 draft which was completed in 2007.
- In response to the 2007 SAB conclusions and recommendations, and public comments, EPA made revisions to the draft Inorganic Arsenic assessment including evaluation of numerous epidemiological studies, implementation of revisions to the cancer modeling, and sensitivity analyses of cancer model assumptions.
- EPA has provided numerous opportunities for public comment (6) and a full and open review of the draft Inorganic Arsenic Toxicological Review.
- EPA seeks a focused SAB review of the responses to several key SAB 2007 recommendations in EPA's 2010 revised draft IRIS Toxicological Review for Inorganic Arsenic.

Outline for Today's Presentations

- History of the Inorganic Arsenic Assessment
  - Santhini Ramasamy
- The 2007 SAB Conclusions and Recommendations, and EPA Revisions
  - Reeder Sams
- Charge to the 2010 Science Advisory Board
  - Peter Preuss

History and Development of the Inorganic Arsenic Assessment

Santhini Ramasamy, PhD, MPH, DABT

Chemical Manager- Office of Water

Background – Arsenic Risk Assessment

- **1988 IRIS Assessment**
  - EPA completed the risk assessment for inorganic arsenic
  - Cancer Slope Factor was derived based on skin cancer effects
- **1999 NRC Report - Arsenic in Drinking Water**
  - EPA requested NRC to evaluate EPA's1988 risk assessment and review and comment on new arsenic toxicity database.
  - NRC derived cancer risk estimates based on bladder cancer effects
- **2001 Arsenic Rule**
  - EPA promulgated the arsenic standard (MCL of 10 ppb) based on NRC 1999 recommendations
- **2001 NRC Report - Arsenic in Drinking Water: 2001 Update**
  - EPA requested NRC to evaluate the new literature since 1999 and reassess the cancer risk estimates reported in the Arsenic Rule

Background – Arsenic Risk Assessment - continued

- **2003** - NCEA initiated revisions to the IRIS assessment for both cancer and noncancer effects
- **2005** - SAB reviewed EPA's draft Toxicological Review for inorganic arsenic - cancer effects only
  - SAB report in 2007
- **2008/2009 -** EPA updated the draft Toxicological Review for inorganic arsenic-cancer effects
  - EPA implemented 2007 SAB recommendations
  - Revised the assessment in response to Agency and Inter Agency Reviewer comments
- **2010 -** EPA released the updated version of the draft Toxicological Review for inorganic arsenic mediated cancer effects in preparation for public comments and SAB review

Overview of Risk Estimation Approach Across Assessments

Data/ Method/ Risk	USEPA 1988	NRC 1999	Arsenic Rule 2001	NRC 2001	USEPA 2005 Draft	US EPA 2010 Draft
Data	Tseng et al. 1968, Tseng, 1977	Wu et al. 1989 Chen et al. 1988, 1992	Wu et al. 1989 Chen et al. 1988, 1992	Wu et al. 1989 Chen et al. 1988, 1992	Wu et al. 1989 Chen et al. 1988, 1992	Wu et al. 1989 Chen et al. 1988, 1992
Endpoint	Skin cancers	Bladder cancers	Lung and Bladder cancers			
Dose Response Model	Linear Multistage, Simple life table	Weibull, Poisson Regression, Simple life table	Multiplicative Poisson, Simple life table	Additive Poisson, BIER IV	Additive Poisson, BIER IV	Additive Poisson, BIER IV

EPA 2010 Implementation of 2007 SAB Recommendations

- Revised the evaluation of epidemiological studies (Section 4.1 and Appendix B)
- Explored the usefulness of MOA Information for supporting the cancer assessment
- Revised the Dose Response Assessment (Section 5.0, Appendix E and F)
  - Followed the study selection and dose response model recommendations
  - Corrected model errors
  - Verified the dose response model results with alternate software (Statistica)
  - Explained the exposure assumptions used to generate cancer risk estimates
  - Conducted sensitivity analysis using alternate exposure assumptions
  - Compared the cancer risk estimates to the findings from other studies (Chile and NE Taiwan) and NRC 2001
  - Evaluated nonlinear models

EPA's Implementation of Revisions in Response to the 2007 SAB's Conclusions and Recommendations

Reeder Sams, PhD

ORD Co-lead- Office of Research and Development

Presentation Format

1) 2005 Charge question presented to the Science Advisory Board

2) Brief summary of Conclusions and Recommendations provided by the 2007 Science Advisory Board to the Administrator

3) EPA's implementation in the 2010 Draft Toxicological Review of Inorganic Arsenic
   - Blue text box indicates specific Section and page references within the 2010 Draft Toxicological Review of Inorganic Arsenic
   - Supplemental information relevant to the specific charge question

2005 Charge Question B3
(Mode of Action)

- Modes of carcinogenic action from exposure to inorganic arsenic: Inorganic arsenic (iAs) undergoes successive methylation steps in humans, resulting in the intermediate production of iAsIII, MMAV, MMAIII, DMAV, and DMAIII. Each arsenical metabolite exhibits its own toxicity.

- Please comment on the conclusion that the available data support the hypothesis that multiple modes of action may be operational following exposure to inorganic arsenic.

Charge Question B3
(2007 SAB Conclusions and Recommendations)

Overall SAB Conclusion(s):

1) **The Panel agrees that multiple modes of action may operate in carcinogenesis induced by inorganic arsenic. This is because there is simultaneous exposure to multiple metabolic products as well as multiple target organs. There are differences in metabolic capability and probably transport into and out of different organs for different metabolic products, so that the composition of the metabolites can differ in different organs as well. Each of the metabolites has its own cytotoxic and genotoxic capability. In general, the pentavalent compounds are less cytotoxic and genotoxic than are the trivalent compounds.**

SAB Recommendation(s):

1) **[regarding the MOA] Taken together, these studies suggest the possibility of a threshold. However, the Panel does not identify what the threshold might be, nor does it describe the shape of the dose-response curve, rather it leaves that to be addressed by EPA in its final assessment based on the outcome of EPA's evaluation of the relevant literature.**

Charge Question B3
(2010 EPA's Implementation)

- In response to the SAB 2007 recommendation, EPA conducted a thorough review of all MOA data available through December 2007 and since that time has scanned literature for information that relates to the MOA.
- EPA's review resulted in a compilation and discussion of MOA studies (Appendix C).
- NRC (1999 & 2001), SAB (2007), and general scientific consensus indicates the carcinogenic MOA (s) are unknown, but there likely exist multiple MOAs
- The Agency concluded that the data concerning a MOA do not define a specific MOA or support the use in quantitative risk assessment

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 4.4.1 Possible Modes of Action and Key Events of Possible Importance (pages 67-93), 4.6.3. Mode of Action Information (pages 98-102); Section Figure 3-1 Traditional Metabolic pathway for iAs in humans (page 16); Table 4-1 (page 71); Appendix C (pages C1-C300).

Table 4-1 from the 2010 Toxicological Review

(Truncated for presentation)

Hypothesized Key Events	Number of Rows in Tables [c]		
	***In Vivo* Human Studies (Table C-1)**	***In Vivo* Experiments Using Laboratory Animals (Table C-2)**	***In Vitro* Experiments (Table C-3)**
Aberrant Gene or Protein Expression[b]	6	32	124
Apoptosis	1	6	78
Cancer Promotion	0	3	3
Cell Cycle Arrest or Reduced Proliferation	0	1	29
Cell Proliferation Stimulation	0	18	21
Chromosomal Aberrations and/or Genetic Instability	13	3	83
Co-carcinogenesis	0	2	3
Co-mutagenesis	0	1	21
Cytotoxicity	0	2	118
DNA Damage	5	6	35

[a] Details of the studies are presented in Appendix C (pages C1-C300).
[b] Some hypothesized key events are shown in boldface to emphasize that in at least one of the tables they contain much more data than the other categories.
[C] Truncated listing of studies reviewed, see Table 4-1(page 71) of the 2010 Toxicological Review

2005 Charge Question C2

(Epidemiology Data)

- Use of human epidemiological data from direct iAs exposure: Since the NRC (2001) report on iAs, an additional body of literature has developed describing epidemiology data from populations in the US exposed to iAs in drinking water.

- Does the SAB agree that the Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans? Please discuss the rationale for your response.

- Do these data provide adequate characterization of the impact of childhood exposure to iAs? Please discuss the rationale for your response.

Charge Question C2
(2007 SAB Conclusions and Recommendations)

SAB Conclusions:

1) Because of various factors (e.g., size and statistical stability of the Taiwanese database relative to other studies, the reliability of the population and mortality counts, the stability of residential patterns, and the inclusion of long-term exposures), this database remains, at this time, the most appropriate choice for estimating bladder cancer risk among humans, though the data have considerable limitations that should be described qualitatively or quantitatively to help inform risk managers about the strength of the conclusions.
2) Regarding childhood exposure to iAs, it was the Panel's view that, based on available data, it is not clear whether children differ from adults with regard to their sensitivity to the carcinogenic effects of arsenic in drinking water….

Charge Question C2
(2007 SAB Conclusions and Recommendations)

SAB Recommendations:

1) Because of various factors (e.g.,..Taiwanese database relative to other studies…) this database remains, at this time, the most appropriate choice for estimating bladder cancer risk among humans, …
2) There are other epidemiologic databases from studies of populations also exposed at high levels of arsenic, and the Panel recommends that these be used to compare the unit risks at the higher exposure levels that have emerged from the Taiwan data.
3) The Panel also suggests that published epidemiology studies of US and other populations chronically exposed from 0.5 to 160 µg/L inorganic arsenic in drinking water be critically evaluated, using a uniform set of criteria and that the results from these evaluations be transparently documented in EPA's assessment documents. If, after this evaluation, one or more of these studies are shown to be of potential utility, the low-level studies and Taiwan data may be compared for concordance. Comparative analyses could lead to further insights into the possible influence of these differences on population responses to arsenic in drinking water.

Charge Question C2
(2010 EPA's Implementation)

- After considering additional studies, EPA concluded that the Taiwanese data were best available data for quantitative analysis

- Additional studies included other areas of high arsenic exposure (e.g., South America) as well as areas of low exposure (e.g., U.S. and Europe)

- Studies systematically evaluated based on uniform criteria:
  - Study type
  - Size of study population
  - Size of control population
  - Relative strengths/weaknesses of study
  - Criteria were evaluated as they were available (study dependent)

- Study summaries are provided in Section 4.1 and in tabular form in Appendix B

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 4.1 Studies in Humans (pages 31-62), 4.7.1. Possible Childhood Susceptibility (pages 102-104); Table 5-5, 5-10,5-11 (page 134, 139, 140); Appendix B (pages B1-B42).

Charge Question C2

(2010 EPA's Implementation)

- Studies examining children and arsenic exposure were evaluated (discussed in Section 4.7.1)
  - Available data do not allow conclusions on differential susceptibility to arsenic exposure between children and adults
  - Recent studies demonstrating potential for cancer after *in utero* exposure were noted and raise concerns regarding arsenic exposure early in development

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 4.1 Studies in Humans (pages 31-62), 4.7.1. Possible Childhood Susceptibility (pages 102-104); Table 5-5, 5-10,5-11 (page 134, 139, 140); Appendix B (pages B1-B42).

Limitations of Epidemiological Studies

- There were a number of epidemiological studies that were evaluated that were positive and negative
- Lack of statistical power in estimating cancer risk
- Less than long term or lifetime exposures
- Exposure Misclassification
- No water arsenic exposure levels in some studies

2005 Charge Question D2
(Low-Dose Extrapolation & Cancer Modeling)

- Implementation of the recommendations of the NRC (2001): EPA has determined that the most prudent approach for modeling cancer risk from exposure to iAs is to use a linear model because there are significant remaining uncertainties regarding which of the metabolite(s) may be the ultimate carcinogenic moiety and whether or not mixtures of toxic metabolites interact at the site(s) of action.

- Does the panel concur with the selection of a linear model following the recommendations of the NRC (2001) to estimate cancer risk at this time? Please discuss your response in light of the highly complex mode of action for iAs with its metabolites.

Charge Question D2
(2007 SAB Conclusions and Recommendations)

SAB Conclusions:

1) Inorganic arsenic has the potential for a highly complex mode of action. Until more is learned about the complex PK and PD properties of iAs and its metabolites there is not sufficient justification for the choice of a specific nonlinear form of the dose-response relationship.

SAB Recommendations:

1) The NRC (2001) recommendation to base risk assessments on a linear dose response model that includes the Southwestern Taiwan population as a comparison group seems the most appropriate approach.
2) The Panel also recommends 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.

Charge Question D2

(2010 EPA's Implementation)

- Available MOA data do not justify non-linear low-dose extrapolation (Section 4.6.3)
- A range of model forms investigated (discussed in Section 5.3). Model used in derivation of preferred risk assessments (see Section 5.3.3) employs:
  - Poisson regression of cancer mortality against age and dose fit by maximum likelihood estimation
  - A quadratic age model
  - A linear dose term
  - Confidence limits on the dose term estimated by profile likelihood estimates derived for the data set including the Taiwan reference population
- Impact of alternative assumptions were investigated through sensitivity analyses including a multiplicative model with a quadratic term for dose (Section 5.3.8.5)

Section References from 2010 iAs Toxicological Review:

Relevant Sections of Tox Review: 4.6.3 MOA Information (pages 98-102), 5.3. Cancer Assessment (oral exposure) (pages 112-145); Appendix C (pages C1-C300); Appendix F (pages F1-F7).

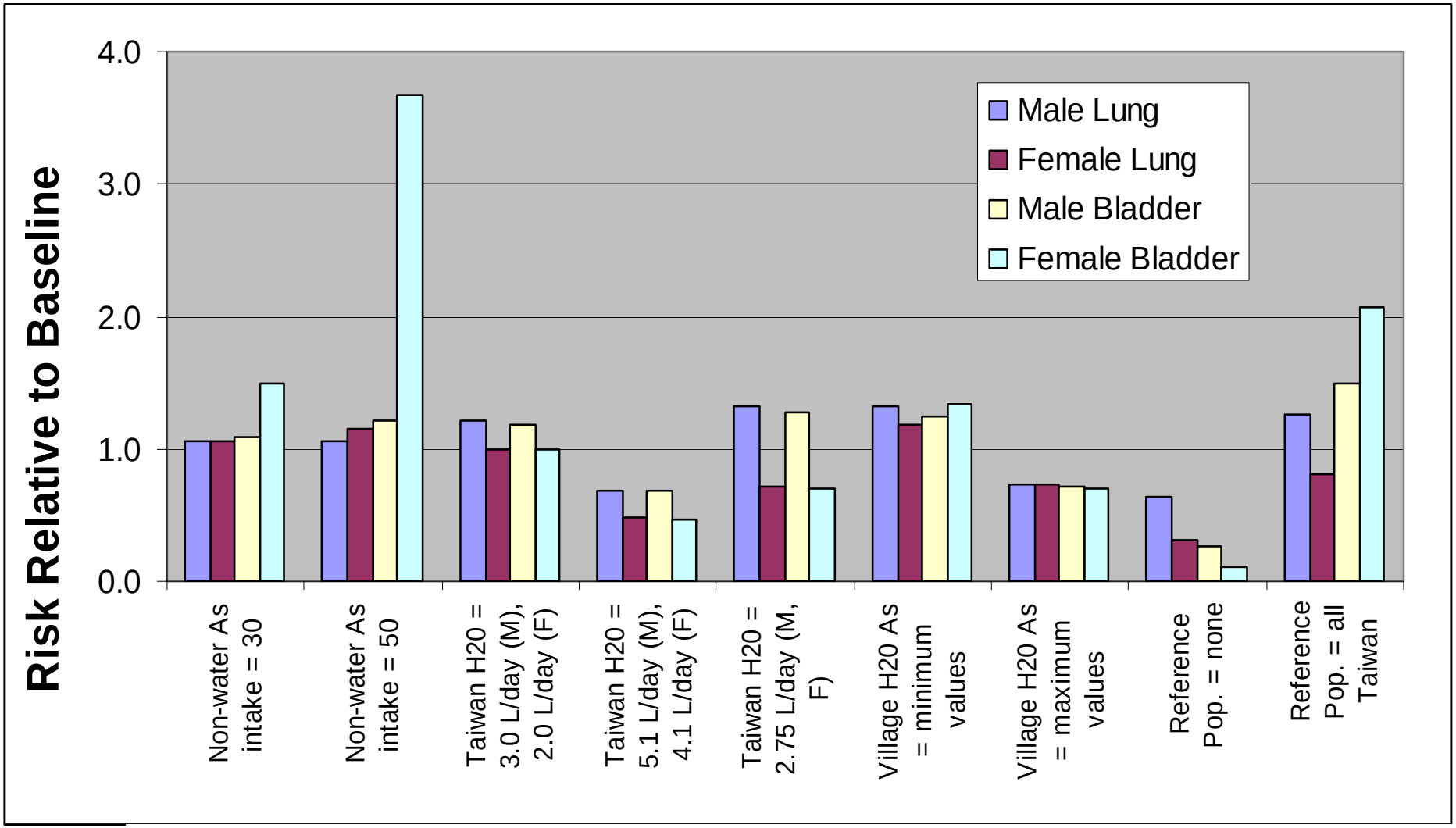
Charge Question D2

(2010 EPA's Implementation & Response)

- Alternative model forms (non-linear) were evaluated and results presented (Section 5.3.8.6)
- Properties of dose-response relationship in low-dose range of Taiwanese data were investigated
  - Arsenic slope coefficients were positive and significant even when high-exposure groups were excluded from analysis
  - Dose-response modeling found no indication of a threshold for arsenic exposure below which cancer risks are not elevated

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 4.6.3 MOA Information (pages 98-102), 5.3. Cancer Assessment (oral exposure) (pages 112-145); Appendix C (pages C1-C300); Appendix E; Appendix F (pages F1-F7).

Figure 5-2.-Change in Arsenic-Related Unit Risk Estimates Associated with Variations in Input Assumptions [a]



[a]Baseline inputs: reference population = southwest Taiwan; male and female body weight = 50 kg, male water intake = 3.5 L/day, female water intake = 2.0 L/day, reference and exposed population non-water arsenic intake = 10 μg/day. U.S. population male and female body weights = 70 kg, male and female water consumption = 2.0 L/day.

2005 Charge Question D3

(Low-Dose Extrapolation & Cancer Modeling)

- EPA re-implemented the model presented in the NRC (2001) in the language R as well as in an Excel spreadsheet format. In addition, extensive testing of the resulting code was conducted.

- Please comment upon precision and accuracy of the re–implementation of the model.

Charge Question D3
(2007 SAB Conclusions and Recommendations)

SAB Conclusions:

1) That the EPA program conformed to the NRC (2001) recommendation for modeling cancer hazard as a function of age and the average daily dose of exposure to arsenic through drinking water sources.
2) The panel did, however, identify and report to the EPA on two potential discrepancies in the data inputs and one computational error in the portion of the program that employs the BEIR-IV formula to evaluate excess lifetime cancer risk from arsenic exposure.

SAB Recommendations:

1) The panel made several suggestions for improvements in the model's programming and documentation conventions as well as recommendations for specific sensitivity analyses designed to test the robustness of the model to alternative formulations of the hazard function and aggregate population data inputs.

Charge Question D3

(2010 EPA's Implementation & Response)

- EPA made a number of changes to the model implementation in response to the SAB comments.
  - Models were implemented in Excel® and replicated using Statistica® (as in the previous analyses, the linear Poisson dose-response models were estimated using maximum likelihood methods)
  - Confidence limits on the arsenic dose-response coefficients were estimated using profile likelihood, rather than Bayesian simulation (estimates were very similar to those obtained using Bayesian simulation and "bootstrap" methods).
  - The BEIR IV formula for estimating lifetime cancer incidence risks was modified - estimates of lifetime cancer incidence data based on "background" cancer incidence and mortality data from the NCI SEER program (see Section 5.3.7.3).
  - The revised approach is discussed in detail in Appendix E.

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 5.3. Cancer Assessment (oral exposure) (pages 112-145); Sensitivity Analyses to test model robustness 5.3.8.5 (pages 137-142); Appendix E (pages E1-E4).

Charge Question D3

(2010 EPA's Implementation)

- As discussed in the response to Charge Question D2, EPA conducted a sensitivity analyses on a number of model parameters. These analyses are described in Section 5.3.8.5.

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 5.3. Cancer Assessment (oral exposure) (pages 112-145); Sensitivity Analyses to test model robustness 5.3.8.5 (pages 137-142); Appendix E (pages E1-E4).

Comparison of Arsenic Oral Cancer Slope Factors (per mg/kg-d) for Lung Cancer and Bladder Cancer in US Populations from NRC (2001) and USEPA 2010

	Male Combined Lung +Bladder	Female Combined Lung +Bladder
National Research Council 2001 Oral Cancer Slope Factor, per mg/kg/day[a]	26	21
2010 iAs Toxicological Review Oral Cancer Slope Factor, per mg/kg/day	16.9	25.7

[a]Oral CSFs (per mg/kg-d) for Lung Cancer and Bladder Cancer in US Populations were derived by EPA from maximum likelihood estimates reported by the NRC (2001), see Section 5.3.8.4.

2005 Charge Question D4
(Drinking Water Consumption)

- Available literature describing drinking water consumption rates for the southwestern Taiwanese study population: NRC (2001) stated that the drinking water consumption rate, as well as variability of that rate in both US and Taiwanese populations, are important factors to consider. In calculating risk estimates for U.S. populations exposed to arsenic through drinking water, NRC used a drinking water consumption rate of 1 L/day for the US population and two possible consumption rates for the Taiwanese population: 1 L/day (identical to the US population) and 2.2 L/day with little or no supporting rationale. Since publication of NRC 2001, a number of new studies have become available and are summarized in the Cancer Slope Factor Workgroup Issue Paper. Agency reviews of the relevant literature suggests that the mean drinking water (for the Taiwanese study population) consumption rate is between 1 to 4.6 L/day. EPA's current cancer modeling includes water intake adjustments for 2.0 and 3.5 L/day.

- What drinking water value does the panel recommend for use in deriving the cancer slope factor for inorganic arsenic?

Charge Question D4
(2007 SAB Conclusions and Recommendations)

SAB Conclusions:

1) Agreed that water consumption assumptions impact the assessment of arsenic risk
2) Panel did not recommend specific values for use in evaluating dose-response in the Taiwanese study or for levels of exposure in the U.S. population risk estimates

SAB Recommendations:

1) Evaluate impact of drinking water consumption rates associated with highly exposed population groups with differing exposures and susceptibilities (e.g., children, pregnant women)
2) Incorporate variability parameters for individual water consumption into dose-response analysis for the Taiwanese population, as was done for the U.S. population
3) Conduct sensitivity analyses on the impact of using a range of consumption values for the Taiwanese population

Charge Question D4
(2007 SAB Conclusions and Recommendations)

- SAB Recommendations:

  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).

Charge Question D4

(2010 EPA's Implementation)

- Data were unavailable on individual water consumption rates and nonwater arsenic intake in the Taiwanese study populations.
- Sensitivity analyses were conducted with ranges of drinking water consumption and nonwater arsenic consumption.
- Risk models also were fit using three different sets of village arsenic drinking water concentrations and three sets of assumptions related to reference populations (results summarized in Table 5-10 and Table 5-11)
  - Cancer slope estimates for male and female lung cancer and male bladder cancer were relatively insensitive to assumptions related to nonwater arsenic intake and varied more or less inversely with the assumed daily water consumption, and with drinking water arsenic concentration estimates
- The cancer slope estimates for female bladder cancer were generally more sensitive to changes in exposure assumptions than the other endpoints

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 5.3.5 Nonwater Arsenic Intake and Drinking Water Consumption (pages 123-125), Sensitivity Analyses to water intake assumptions 5.3.8.5 (pages 137-142); Table 5-10 & Table 5-11 (page 139) .

Table 5-11 -Proportional Changes in Cancer Risks at 10 µg/L Associated With Changes in Modeling Inputs and Assumptions

Modeling Assumptions/Input Values	Male Lung	Female Lung	Male Bladder	Female Bladder
Baseline (all default values)[a]	0%	0%	0%	0%
Non-water As intake = 0 µg/day (reference and exposed populations)	0%	-4%	-6%	-13%
Non-water As intake = 30 µg/day (reference and exposed populations)	5%	6%	9%	50%
Non-water As intake = 50 µg/day (reference and exposed populations)	5%	15%	22%	267%
Non-water As intake (exposed population) = 0 µg/day	0%	0%	0%	0%
Non-water As intake (exposed population) = 100 µg/day	-5%	-8%	-6%	-7%
Non-water As intake (exposed population) = 200 µg/day	-11%	-19%	-13%	-20%
Taiwan H_20 consumption = 3.0 L/day (M), 2.0 L/day (F)	21%	0%	19%	0%
Taiwan H_20 consumption = 5.1 L/day (M), 4.1 L/day (F)	-32%	-52%	-31%	-53%
Taiwan H_20 consumption = 2.75 L/day (M, F)	32%	-29%	28%	-30%
Village H_20 As concentrations = minimum values	32%	19%	25%	33%
Village H_20 As concentrations = maximum values	-26%	-27%	-28%	-30%
Reference population = none	-37%	-69%	-74%	-88%
Reference population = all Taiwan	26%	-19%	50%	107%

[a]Baseline inputs: reference population = southwest Taiwan; male and female body weight = 50 kg, male water intake = 3.5 L/day, female water intake = 2.0 L/day, reference and exposed population non-water arsenic intake = 10 µg/day. U.S. population male and female body weights = 70 kg, male and female water consumption = 2.0 L/day.

2005 Charge Question D5
(Dietary Intake)

- Selection of an estimate of dietary intake of arsenic from food: The issue of intake of arsenic from food (e.g., dry rice, sweet potatoes) has been distinguished from the issue of intake of arsenic from drinking water. The NRC addressed the issue of arsenic in food by determining how sensitive the calculation of ED01 was to the consumption rate. NRC found that changing the consumption rate from 50 µg/day to 30 µg/day did not change the calculated ED01 significantly (about 1% difference). Since the publication of NRC 2001, a number of new studies have become available, summarized in the Cancer Slope Factor Workgroup Issue Paper. EPA's current cancer modeling includes dietary intake adjustments for 0, 10, 30, and 50 µg/day.

- What background dietary intake (of arsenic) value does the panel recommend for both the control population and study population

Charge Question D5
(2007 SAB Conclusions and Recommendations)

SAB Conclusions:

1) Agreed that arsenic levels in food are important considerations for assessing lung and bladder cancer risk associated with exposures to arsenic in drinking water

SAB Recommendations:

1) Panel 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
2) Recommendations for analytical steps to clarify impact of food levels of arsenic on dose-response and exposure as it revises risk estimates:
   - Conduct sensitivity analyses using a range of total arsenic food intake values from at least 50 to 100 µg /day to perhaps as high as 200 µg/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.
   - Not assume that the control population has an intake value of zero arsenic from food.
   - Apply greater rigor in their discussions of data used in these assessments (e.g., sources, methodological and analytical issues, bioavailability).
   - Give immediate research attention to the issue of arsenic bioavailability.

Charge Question D5

(2010 EPA's Implementation)

- As discussed in the response to Charge Question D4, sensitivity analyses were conducted that assumed nonwater arsenic intakes (doses) for the exposed populations ranging from 0 to 200 µg/day and ranging from 0 to 50 µg/day in the reference population.

- Sensitivity analyses to specifically address arsenic bioavailability were not conducted, as the range of absorbed dose that was evaluated implicitly addresses potential bioavailability differences. This range of arsenic intake was considered to cover the plausible ranges of nonwater dietary arsenic and bioavailability thereof.

Section References from 2010 iAs Toxicological Review:
Relevant Sections of Tox Review: 5.3.5 Nonwater Arsenic Intake and Drinking Water Consumption (pages 123-125), Sensitivity Analyses to nonwater intake assumptions 5.3.8.5 (pages 137-142); Table 5-10 & Table 5-11 (page 139) .

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Reference population = none	-37%	-69%	-74%	-88%
Reference population = all Taiwan	26%	-19%	50%	107%

[a]Baseline inputs: reference population = southwest Taiwan; male and female body weight = 50 kg, male water intake = 3.5 L/day, female water intake = 2.0 L/day, reference and exposed population non-water arsenic intake = 10 µg/day. U.S. population male and female body weights = 70 kg, male and female water consumption = 2.0 L/day.

Charge to the 2010 Science Advisory Board

Peter Preuss, PhD

Director, National Center for Environmental Assessment,

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2010 Charge to Science Advisory Board Panel

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

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

- EPA concluded that the Taiwanese data were the best available for determining the carcinogenic risk due to exposure to iAs.
- In response to SAB recommendations:
  - EPA performed an extensive review and evaluation of all available human studies for iAs using the criteria suggested by the SAB (summarized in Section 4.1 and 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).

2010 Charge to Science Advisory Board Panel

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

- SAB noted the possibility of a nonlinear dose-response at low exposures, but recommended use of a linear low dose extrapolation approach to determine the cancer risk for iAs from the Taiwanese dataset due to uncertainty in the MOA.
- SAB suggested 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).
- SAB concluded that overall, EPA had implemented the recommended modeling by NRC (2001), and recommended 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
  - EPA conducted a sensitivity analysis of nonlinear forms of the dose-response in the 2010 draft IRIS assessment.

2010 Charge to Science Advisory Board Panel

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

- SAB did not recommend specific values for the exposure assumptions or parameters used in the cancer model.
- SAB recommended:
  - evaluating the impact on the cancer risk of using a range of values,
  - assessing the variability
  - conducting a sensitivity analysis for exposure parameters (e.g., water intake, background dietary exposure).

- EPA responded to SAB recommendations by:
  - evaluating the impact on the estimated cancer risk of using a range of exposure parameter values (e.g., water intake, background dietary exposure)
  - assessing variability
  - conducting 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.

Summary

- The current draft of the Inorganic Arsenic assessment has been underway since 2003; the SAB reviewed the 2005 draft which was completed in 2007.
- In response to the 2007 SAB conclusions and recommendations, and public comments, EPA made revisions to the draft Inorganic Arsenic assessment including evaluation of numerous epidemiological studies, implementation of revisions to the cancer modeling, and sensitivity analyses of cancer model assumptions.
- EPA has provided numerous opportunities for public comment (6) and a full and open review of the draft Inorganic Arsenic Toxicological Review.
- EPA seeks a focused SAB review of the responses to several key SAB 2007 recommendations in EPA's 2010 revised draft IRIS Toxicological Review for Inorganic Arsenic.

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Supplemental Slides

Epidemiological Study Criteria

SAB Recommendations

- Study type
- Size of the study population and control population
- Exposure Misclassification
  - Temporal variability in assigning past arsenic levels from recent measurements
  - Extent of reliance on imputed exposure levels
- Number of persons exposed at various estimated levels of water-borne arsenic
- Study response/participation rates
- Control selection methods in case control studies
- Relative strengths and weaknesses of the study
- Resulting influence of these factors on the magnitude and statistical stability of cancer risk estimates
- Present the results in narrative and tabular format

Epidemiological Study Criteria

2010 Tox Review

- Study period
- Subjects/Control (included study size)
- Exposure Assessment
  - Drinking water arsenic measurements
  - Nail arsenic
- Study outcome
  - Odds ratio, SMR, SIR
- Strengths and weaknesses
  - Exposure misclassification
  - Temporal variability in assigning past arsenic levels from recent measurements
  - Study response/participation rates
  - Extent of reliance on imputed exposure levels
  - Control selection methods in case control studies
  - Potential confounders
  - Recall/Selection bias
  - Dose response information
- Presented the results in narrative and tabular format

Alternate/Nonlinear Dose Response Models

- Quadratic form – Dose

  $h(x,t)=Exp(a1+a2*age+a3*age^2)*(1+b1*dose+b2*dose^2)$

- Exponential Linear Dose

  $h(x,t)=Exp(a1+a2*age+a3*age^2)*Exp(b0+b1*\ dose)$

- Exponential Quadratic Dose

  $h(x,t)=Exp(a1+a2*age+a3*age^2)*Exp(b0+b1*dose+b2*dose^2)$

SW Taiwanese Database

- Strengths
  - Size and statistical stability of the database relative to other studies
  - Reliability of the population and mortality counts
  - Stability of the residential patterns
  - Inclusion of long term exposures
  - Inclusion of low doses
- Weaknesses
  - Ecological thus no individual exposure assessment available

Mode of Action

- Aberrant gene or protein expression
- Apoptosis changes
- Cell proliferation
- Cell cycle arrest
- Cytotoxicity
- DNA damage
- DNA repair inhibition or stimulation
- Oxidative stress
- Immune system changes
- Signal transduction
- Sulfhydryl binding

Human Data - MOA

- Chromosomal aberrations (13)
- Aberrant gene expression (6)
- DNA damage (5)
- Oxidative Stress (2)
- DNA methylation (3)

Ref: Table 4-1 Inorganic Arsenic Tox Review – Cancer

Numbers in the parenthesis refer to the number of studies/observations

Animal Data MOA

- Aberrant gene expression (32)
- Oxidative Stress (30)
- Cell proliferation stimulation (18)
- Apoptosis (6)
- DNA damage (6)

Ref: Table 4-1 Inorganic Arsenic Tox Review – Cancer

Numbers in the parenthesis refer to the number of studies/observations

In Vitro MOA

- Chromosomal aberrations (83)
- DNA damage (35)
- Signal transduction (51)
- Immune system response (46)
- Aberrant gene expression (124)
- Apoptosis (78)
- Cell cycle arrest (29)
- Cell proliferation stimulation (21)
- Cytotoxicity (118)
- Oxidative Stress (69)

Source: Inorganic Arsenic Tox Review – Cancer, Table 4-1

Numbers in the parenthesis refer to the number of studies/observations

Arsenic Cancer Risk Model

- Model Fit - Poisson Model
  - $h(x,t) = h0(t) \times g(x)$
    - $h(x,t)$ = cancer mortality risk at dose “x” and age “t”
    - $h0(t)$ = cancer mortality risk in the reference population at age “t”
    - $g(x)$ = risk attributable to arsenic exposure at dose “x” (mg/kg-day)
  - $h(x,t) = Exp(a1 + a2 \times age + a3 \times age2) \times (1 + b \times dose)$

    a1, a2, a3 = age coefficients; b = dose coefficient
- BIER IV Model
  - Cancer Risk for US populations

Comparison of Cancer Slope Factors

Assessment	CSF (per mg/kg/day)			
	Bladder		Lung	
	Male	Female	Male	Female
NRC 2001[a]	16	8	10	13
2010 Cancer Tox Review	11.2	10.5	6.7	16.6

Source: 2010 Arsenic Toxicological Review, Table 5-3 & 5-9

aOral CSFs (per mg/kg-d) for Lung Cancer and Bladder Cancer in US Populations were derived by EPA from maximum likelihood estimates reported by the NRC (2001), see Section 5.3.8.4.

Sensitivity Analysis Parameters

- Background arsenic intake : 0, 10, 30 and 50 µg/day (reference and exposed population)
- Background arsenic intake (0, 100 and 200 µg/day (exposed population)
- SW Taiwanese water consumption
  - Males (2.75, 3.0, 3.5, 5.1 L/day)
  - Females (2.0, 2.75, 4.1 L/day)
- SW Taiwanese village water arsenic concentration (minimum, maximum and median)
- Reference Population (None, SW Taiwan and all Taiwan)