

SAB 10/25/2010 Draft
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This report does not represent EPA policy



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

1 The Honorable Lisa P. Jackson
2 Administrator
3 U.S. Environmental Protection Agency
4 1200 Pennsylvania Avenue, N.W.
5 Washington, DC 20460
6

7 Subject: Review Comments on EPA's Responsiveness to SAB 2007 Recommendations for
8 the Revision of Cancer Assessment of Inorganic Arsenic
9

10 Dear Administrator Jackson:
11

12 The Science Advisory Board (SAB) received a request from the Office of Research and
13 Development's National Center for Environmental Assessment to evaluate and comment on the
14 agency's implementation of the SAB 2007 recommendations regarding EPA's revision of the
15 cancer assessment of inorganic arsenic. In response, a work group of the chartered SAB was
16 convened to review the agency's document entitled *Toxicological Review of Inorganic Arsenic:*
17 *In Support of the Summary Information on the Integrated Risk Information System (IRIS)*
18 (EPA/635/R-10/001), focusing on three areas: evaluation of epidemiological literature; dose-
19 response modeling approaches; and the sensitivity analysis of the exposure assumptions used in
20 the risk assessment. The SAB was not asked to conduct a full peer review of the assessment,
21 including EPA's calculation of the cancer risk estimate.
22

23 The SAB commends the agency on its efforts to be responsive to our previous 2007
24 recommendations. In keeping with SAB practice, presentations by EPA representatives and
25 comments from members of the public were considered during the development of this report.
26 The SAB has made a number of recommendations to improve the clarity and transparency of the
27 2010 draft assessment and to strengthen the scientific basis of EPA's findings and conclusions.
28 Key recommendations are highlighted below.
29

30 In 2007, the SAB recommended the use of the epidemiologic data on the Taiwanese
31 population for estimating human cancer risk from exposure to inorganic arsenic. The SAB also
32 suggested that the agency consider other epidemiologic studies from the United States and other
33 countries, utilizing a uniform set of evaluative criteria. The SAB supports its previous
34 recommendations that the Taiwanese dataset remains the most appropriate data set for
35 determining the cancer risk from exposure to inorganic arsenic. Although EPA's 2010 draft
36 assessment presents a comprehensive overview of the epidemiological literature on arsenic and
37 cancer up to 2007, it needs to more clearly state the set of criteria that EPA used in evaluating
38 and presenting the studies. Where possible, the summaries of the epidemiology studies should
39 include a quantitative presentation or discussion of the relative risk point estimates and the
40 associated confidence intervals. Additionally, EPA should consider including an addendum or
41 appendix describing major epidemiology studies that were published since 2007.

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5 advisory committee providing extramural scientific information and advice to the Administrator and
6 other officials of the Environmental Protection Agency. The Board is structured to provide balanced,
7 expert assessment of scientific matters related to problems facing the Agency. This report has not
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2 **Science Advisory Board**
3 **Arsenic Cancer Review Work Group**
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U.S. Environmental Protection Agency
Science Advisory Board
Chartered Board
(To be updated)

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EXECUTIVE SUMMARY

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

Evaluation of epidemiological data

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

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

Mode-of-action

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

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

8
9 *Sensitivity analysis of dose-response modeling*

10
11 In 2007, the SAB recommended that EPA consider using alternative dose-response
12 models and perform a sensitivity analysis of the Taiwanese data with different exposure metrics,
13 with the subgroup of villages with more than one well measurement and using a multiplicative
14 model that includes a quadratic term for dose. The SAB finds that the sensitivity analysis of dose-
15 response modeling presented in the 2010 draft assessment was responsive to the SAB previous
16 recommendations. The SAB agrees with the conclusion that none of the alternative models (i.e.,
17 quadratic, quadratic exponential and linear exponential) evaluated by EPA materially changed the
18 estimated risk levels versus use of a linear model. The EPA also evaluated whether the models
19 were inordinately affected by the high end of the dose-response curve and found that they were
20 not. However, the SAB believes that more transparency and a better scientific rationale for the
21 agency's selection process are needed. To improve the clarity and transparency of the draft
22 assessment, there are a number of aspects of the sensitivity analysis that should be described in
23 greater detail. They include the need for a more detailed description of the Taiwanese datasets
24 used in developing the risk model; a better description of the distribution of well water arsenic
25 concentrations across and within the 42 exposed villages; and a further explanation of the
26 sensitivity displayed for female bladder cancer risks. The SAB notes that, while EPA's choice of
27 a linear approach is consistent with EPA's risk assessment procedures, it has produced a
28 calculated upper-bound cancer risk estimate for arsenic that is of significant public health
29 concern. The SAB suggests that EPA discuss, possibly in other EPA complete risk assessment
30 documents, how the estimated risks for arsenic should be interpreted in light of current estimated
31 bladder and lung cancer incidence for the U.S. population.

32
33 *Exposure assessment and sensitivity analysis*

34
35 The 1999 NRC noted that the assessment of arsenic exposure via drinking water is often
36 based on the measurements of arsenic concentrations in drinking water and assumptions regarding
37 the amount of water consumed. The 2001 NRC added that the method used to characterize
38 arsenic dose in a study is a source of uncertainty in arsenic dose-response assessment.
39 Furthermore, the NRC noted that the choice of the dose measurement affects the interpretation of
40 an epidemiological study and the choice of the dose-response model. The 2007 SAB agreed that
41 water consumption (via drinking water, in beverages, or in cooking water) assumptions could
42 have an impact on the assessment of arsenic's risk. However, the 2007 SAB did not recommend
43 specific values for EPA to use in evaluating dose-response in the Taiwanese study nor for levels
44 of exposure in the U.S. population risk estimates. It instead recommended that uncertainty in
45 exposure parameters be evaluated for both the Taiwanese study population and the U.S.
46 populations through sensitivity analyses. The 2007 SAB recommended that EPA evaluate the

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1 drinking water consumption rate assumptions used with regard to highly exposed and sensitive
2 subpopulations. Additionally, the NRC (2001) recommended that EPA consider the background
3 dietary intake of inorganic arsenic and incorporate the adjustment values. The 2007 SAB also
4 concluded that arsenic levels in food are important considerations for EPA's assessment of lung
5 and bladder cancer risk associated with exposures to arsenic in drinking water. The 2007 SAB
6 stated that a range of total arsenic food intake values should be included in the sensitivity
7 analyses.
8

9 The SAB finds EPA's revisions to the IRIS assessment to be partially responsive to SAB's
10 2007 recommendations regarding the exposure assumptions. The SAB provides two primary
11 general suggestions for improving the responsiveness of the assessment; they include, making
12 more transparent the scientific basis of the exposure assumptions used; and enhancing the rigor
13 and transparency of the sensitivity analysis. The basic approach to the sensitivity analysis is
14 adequate for meeting the minimum requirements for the intended purpose, and is responsive to
15 the SAB recommendation in that the impact of choice of assumptions is shown in terms of
16 specific cancer risks (lung and bladder, males and females). There are sufficient data to support
17 development of variability and/or uncertainty distributions for some inputs, such as drinking
18 water consumption rates in the United States, but the data are not available to assign
19 corresponding distributions for the Taiwanese populations.
20

21 The SAB notes that much of the documentation addressing the scientific basis of the
22 exposure assumptions is available through separate documents (e.g. EPA Issues Paper) that, if
23 incorporated within the agency's draft IRIS assessment, will help address the SAB's concerns.
24 The SAB recommends that relevant information from these documents be integrated within the
25 current document as appropriate with the goal of enhancing transparency and scientific
26 credibility. The SAB has provided specific suggestions, within the body of the report, for making
27 the scientific basis of the exposure assumptions used more transparent and for enhancing the rigor
28 and transparency of the sensitivity analyses.
29

1 BACKGROUND

2
3 Arsenic is a naturally occurring element that is found throughout the environment.
4 Exposure to inorganic arsenic can result in different health outcomes depending upon the route of
5 exposure. Arsenic compounds are used as a mordant in the textile industry, for preserving hides,
6 as medicinal uses, pesticides, pigments, and wood preservatives. EPA's health effects assessment
7 for inorganic arsenic was first made available on the Integrated Risk Information System (IRIS)
8 database in 1988. Various committees have reviewed aspects of the EPA's revised assessment of
9 cancer risk associated with exposure to inorganic arsenic. They include two National Research
10 Council (NRC) committees (1999, 2001) that concluded that the cancer risk for inorganic arsenic
11 should be based on internal cancers (lung and bladder) instead of skin cancers. In 2005, the SAB
12 was asked to review several EPA documents including:

- 13
- 14 • Office of Pesticide Programs' (OPP) *Draft Science Issue Paper: Mode-of-action for*
15 *Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response*
16 *Extrapolation* (U.S. EPA OPP, 2005a)
- 17 • Office of Research and Development (ORD) Issue Paper *Cancer Risk Assessment for*
18 *Organic Arsenical Herbicides: Comments on Mode of Action, Human Relevance and*
19 *Implications for Quantitative Dose-Response Assessment* (Appendix E of U.S. EPA OPP,
20 2005, USEPA ORD, 2005b).
- 21 • Office of Water's (OW) *Draft Toxicologic Review of Inorganic Arsenic* (U.S. EPA OW,
22 2005c).

23
24 At that time, the SAB convened a panel of experts to provide advice on the metabolism,
25 mode of action, dose-response, and approaches to low-dose extrapolation of cancer risk for
26 Dimethylarsinic Acid (DMA^v) and inorganic arsenic (iAs). The SAB review report (EPA-SAB-
27 07-008) was issued in June 2007 and is available at
28 <http://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/EADABBF40>
29 [DED2A0885257308006741EF/\\$File/sab-07-008.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/EADABBF40).

30
31 In 2010, ORD's National Center for Environmental Assessment (NCEA) requested the
32 SAB evaluate and comment on EPA's implementation of SAB (2007) key recommendations in
33 the 2010 draft assessment entitled, *Toxicological Review of Inorganic Arsenic: In Support of the*
34 *Summary Information on the Integrated Risk Information System (IRIS)* (EPA/635/R-10/001). In
35 response to this request, the SAB convened a workgroup of the chartered Board to comment on
36 the agency's charge questions that focused on three areas: evaluation of epidemiological
37 literature; dose-response modeling approaches; and the sensitivity analysis of the exposure
38 assumptions used in the risk assessment. The SAB was not asked to conduct a full peer review of
39 the assessment, including EPA's calculation of the cancer risk estimate. The SAB workgroup
40 held a public face-to-face meeting on April 6-7, 2010 to discuss and deliberate on its responses to
41 EPA's charge questions. The chartered Board conducted a quality review of the work group's
42 draft report (May 13, 2010) at a public teleconference on June 16, 2010. This SAB draft report
43 incorporates the SAB quality review comments and public comments, both written and oral,
44 which were received throughout the advisory process.

1 **RESPONSES TO EPA’S CHARGE QUESTIONS**

2 **Charge Question 1:**

3
4 *The SAB concluded that the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992)*
5 *remains the most appropriate dataset to determine carcinogenic risk due to exposure to iAs. They*
6 *recommended that EPA should evaluate other published epidemiology studies using a uniform set*
7 *of criteria and document these findings in the assessment. They also stated that if one or more*
8 *studies provide potential utility, comparisons should be provided in the assessment.*
9

10 *EPA agreed that the Taiwanese data were the best available for determining the*
11 *carcinogenic risk due to exposure to iAs. In response to SAB’s recommendation, an extensive*
12 *review and evaluation of all available human studies for iAs using the criteria suggested by the*
13 *SAB was performed by EPA and is summarized in Section 4.1 of the draft IRIS assessment and*
14 *included in tabular format in Appendix B. EPA concluded in the 2010 draft IRIS assessment that*
15 *there were no additional epidemiological studies that had comparable utility to the Taiwanese*
16 *dataset (Wu 1989; Chen et al., 1988, 1992).*
17

18 **Please comment on EPA’s response to the recommendations and the conclusions of the SAB**
19 **(2007) Arsenic panel regarding the evaluation of the epidemiological literature.**
20

21 **Response:**

22
23 In 1999, the NRC concluded that ecological studies from the arsenic endemic area of
24 Taiwan provide the best available empirical human data for assessing the risks of arsenic-induced
25 cancer. The 2001 NRC also concluded that the data from southwestern Taiwan remain
26 appropriate for use in dose-response assessment of arsenic in drinking water. In 2007, the SAB
27 supported the use of the epidemiologic data on the Taiwanese population for estimating human
28 cancer risk for inorganic arsenic especially to identify the potential range of responses of human
29 populations. The 2007 SAB urged the agency to consider other epidemiologic studies from the
30 United States and other countries, utilizing a uniform set of evaluative criteria, as they develop
31 their risk assessment. The 2007 SAB recommended consideration of the following additional
32 factors when reviewing the studies:
33

- 34 1. Estimates of the level of exposure misclassification;
35 2. Temporal variability in assigning past arsenic levels from recent measurements;
36 3. The extent of reliance on imputed exposure levels;
37 4. The number of persons exposed at various estimated levels of waterborne arsenic;
38 5. Study response/participation rates;
39 6. Estimates of exposure variability;
40 7. Control selection methods in case-control studies; and
41 8. The resulting influence of these factors on the magnitude and statistical stability of risk
42 estimates.
43

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1 The SAB concludes that EPA has been responsive to the 2007 SAB recommendations in
2 evaluating the epidemiology studies published through 2007. The 2010 draft IRIS assessment
3 presents a well organized and very comprehensive overview of the epidemiological literature on
4 arsenic and cancer through 2007. The SAB recognizes that there are limitations that are inherent
5 in the design of environmental epidemiological investigations, particularly regarding
6 reconstruction of past exposure levels. EPA has described the limitations of each study in Section
7 4.1 of the draft IRIS assessment, and presented a summary of study strengths and limitations in
8 the tables of Appendix B. The systematic review of the literature, however, needs to more clearly
9 state the set of criteria that were used in evaluating the studies. Additional clarification and
10 documentation on how various study design factors were considered and weighted in the
11 evaluation are needed. In addition, there are aspects of studies that are discussed in Section 4.1
12 narrative that are not included in the summary table of Appendix B. The SAB recommends that
13 the tables in Appendix B be reformatted to present the study summaries more clearly and in a
14 more consistent format including pulling any essential information from references into the text
15 for clarity.
16

17 The SAB supports the 2007 SAB conclusion that the Taiwanese dataset (Wu 1989; Chen
18 et al., 1988, 1992) remains the most appropriate data set for determining the population risk of
19 cancer to exposure to inorganic arsenic. The limitations of the Taiwanese studies are well
20 presented, particularly regarding the ecologic study design, use of death certificates, and
21 assumptions regarding lifetime individual arsenic exposure. The strengths of these studies include
22 availability of community drinking water exposure levels, large populations and person-years of
23 follow-up, and consideration of important potential confounders including socioeconomic status,
24 lifestyle, dietary patterns, and medical care. The SAB acknowledges the concerns expressed
25 regarding the limitations of the Taiwanese dataset; however given the fundamental mission of
26 EPA to protect public health, these well conducted and extensively reviewed studies remain the
27 most appropriate critical studies.
28

29 The SAB received public comments that suggested when comparing the large number of
30 epidemiological studies that demonstrate varying results the power calculations for the studies can
31 provide important insights and should be taken into consideration. The power of an
32 epidemiological study is the probability of detecting an association of a specified strength
33 between exposure and disease if one exists. For example, in studies where statistical significance
34 is not achieved, failure to identify an association may be a reflection of a limitation of the power
35 of the study. The SAB, however, notes that while the relative power of various studies is important
36 to convey, this should not be done by presenting only power calculations. Power calculations are
37 useful in planning a study, but after the study is completed, the most informative presentation of
38 epidemiologic findings that combines both the observed results and reflects the power of the study is
39 the relative risk (RR) point estimates for a specified exposure comparison and the associated
40 confidence intervals. Furthermore, systematic presentation of numbers of individuals in each exposure
41 stratum provides the reader with a sense of relevant sample size within strata and the robustness of the
42 exposure contrast. For instance, the required sample size should be larger when a smaller range of
43 exposures is observed (e.g., the U.S. studies), since the expected magnitude of the RR for low-level
44 exposure is lower. The SAB also recognizes that many published arsenic studies may not present
45 specific power calculations or RR and that a detailed quantitative comparison is difficult. Where
46 possible, the summaries of the epidemiology studies should include a quantitative presentation or

1 discussion of the relative risk point estimates for a specific exposure comparison and the associated
2 confidence intervals. This should be included both in the study descriptions in Section 4.1 and in
3 the table of studies in Appendix B.
4

5 As noted by public comments, the SAB agrees that failure to control potential confounders
6 or misclassification of study population exposure levels may bias study results. In the
7 presentation of one of the critical epidemiology studies (Chen et al. 1992), the IRIS assessment
8 (p.38) states, “a weakness of the study is the assumption that an individual’s arsenic intake
9 remained constant from birth to the end of the follow-up period; this flaw possibly led to the
10 underestimation of risk.” Other epidemiological studies also had similar issues. Indirect
11 measures of individual exposure were used to estimate population exposure levels for all of the
12 epidemiology studies. In Section 4.1, the narrative presenting the epidemiology studies should
13 include a more detailed discussion of bias including literature citations addressing the potential
14 for bias, both underestimating and overestimating of risk, due to confounders or limitations in
15 exposure estimation. Emphasis should be given to estimating the quantitative consequences of any
16 bias. While the existence of bias can usually be proposed with some certainty, the key issue is
17 whether the quantitative consequences of bias are of sufficient magnitude to be of concern. Methods
18 are available for this purpose (see, for example: Lash, Fox, and Fink: *Applying Quantitative Bias
19 Analysis to Epidemiological Data*, Springer, 2009). The SAB suggests that the IRIS assessment
20 include a simple table that identifies potential biases (misclassification of exposure,
21 misclassification of disease, omitting confounders, etc.) and the potential magnitude and direction
22 of bias in inferences that are drawn from the study data. A simple summary could then relate these
23 sources of bias to their impact in the data and methods used in the IRIS assessment.
24

25 The IRIS 2010 assessment includes an extensive review of published epidemiology
26 studies up to and including the year 2007. The SAB recognizes that the assessment cannot be
27 continually updated with every newly published paper and it is not the purpose of IRIS to provide
28 real time summaries of advancing science. However, given the large amount of ongoing research
29 on the health effects of arsenic, the SAB has concerns about the 2007 cutoff. In order to ascertain
30 if new studies will impact the 2010 assessment, EPA should consider including an addendum or
31 appendix describing major epidemiology studies published since 2007 (i.e., those studies that can
32 influence the dose-response assessment due to large sample size or effect estimate that is
33 substantially different from that estimated by Chen et al. (1988, 1992).
34
35

36 Charge Question 2:

37
38 *The SAB noted the possibility of a nonlinear dose-response at low exposures, but due to*
39 *uncertainty in the mode-of-action (including pharmacokinetics and dynamics) the use of a linear*
40 *low dose extrapolation approach to determine the cancer risk for iAs was recommended using*
41 *cancer incidence from the Taiwanese dataset. In addition, the SAB stated that EPA should*
42 *perform a sensitivity analysis for the variables in the cancer modeling with respect to the*
43 *Taiwanese dataset (i.e., exposure metrics, subgroup of villages with more than one well*
44 *measurement, and a multiplicative model that includes a quadratic term for dose). The SAB*
45 *concluded that overall, EPA had implemented the recommended modeling by NRC (2001). Also,*

1 *the SAB made recommendations to perform a sensitivity analysis regarding the robustness of the*
2 *model and alternative formulations.*

3
4 *Consistent with the SAB recommendations, EPA used a linear low-dose extrapolation*
5 *approach and conducted a sensitivity analysis of nonlinear forms of the dose-response in the*
6 *2010 draft IRIS assessment. EPA also explored nonlinear forms of the dose-response from the*
7 *Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992). Sensitivity analyses using alternative*
8 *dose-response models produced potency estimates similar to the linear approach.*

9
10 **Please comment on EPA’s response to the SAB’s recommendations and conclusions**
11 **regarding the approach to modeling inorganic arsenic cancer risks and the corresponding**
12 **sensitivity analyses.**

13
14 **Response:**

15
16 *Mode-of-action and Dose-Response Modeling*

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

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

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

1 *Sensitivity Analysis*

2 The 2007 SAB recommended that EPA perform a sensitivity analysis of the Taiwanese
3 data with different exposure metrics, with the subgroup of villages with more than one well
4 measurement and using a multiplicative model that includes a quadratic term for dose. The SAB
5 finds that the sensitivity analysis of dose-response modeling presented in the 2010 IRIS
6 assessment was responsive to the previous 2007 SAB recommendations. Specifically, EPA was
7 asked to evaluate a model using a quadratic term for dose. EPA evaluated the differences
8 between a linear model and three non-linear models: quadratic, quadratic exponential and linear
9 exponential. Results are described on p. 143, which concludes that “within the range of
10 exposures covered by the epidemiological data, the alternative forms predict very similar risks.”
11 It would be very helpful if the results could be shown graphically, e.g., by showing the dose-
12 response data and model dose-response curves for selected endpoints and age and gender classes.
13 The SAB agrees with the conclusion that none of the alternative models materially changed the
14 estimated risk levels versus use of a linear model. The EPA also evaluated whether the models
15 were inordinately affected by the high end of the dose-response curve. They were not. This was
16 evaluated by running the models without the highest exposure group. EPA evaluated whether
17 exclusion of a reference population influenced the dose-response curve. Results of this analysis
18 (see Fig. 5-2) suggest that exclusion of the reference population did have an effect on risk
19 estimates. EPA evaluated the pros and cons of including a comparison population in a 2005
20 issues paper (Issue Paper: Inorganic Arsenic Cancer Slope Factor, Final Draft, July 23, 2005).
21 The SAB recommends that the rationale from the issue paper be included in the draft IRIS
22 assessment, and the reference population described in greater detail. This will provide more
23 transparency and strengthen the scientific rationale for the agency’s selection process.
24

25 To improve the clarity and transparency of the draft IRIS assessment, there are a number
26 of aspects of the sensitivity analysis that should be described in greater detail. They include:
27

- 28 • **More detailed description of underlying data.** The assessment would benefit from a
29 more detailed description of the Taiwanese datasets used in developing the risk model.
30 The datasets are briefly described in section 4.1.1 as part of the review of the Chen et al.
31 1988a, 1992 and Wu et al., 1989 studies, and key features are summarized in Table B-1.
32 However, readers are required to piece together this information on their own in order to
33 understand the basis for the risk modeling presented in section 5.3.
34
- 35 • **Variability of well water arsenic concentrations.** The distribution of well water arsenic
36 concentrations across and within the 42 exposed villages is not adequately described. Only
37 medians and ranges across the whole set of villages are presented in Table B-1. While the
38 assessment mentions that the number ranged from 2 – 47 measurements, the variability of
39 measurements both within and across wells within a given village is not provided. This
40 information needs to be presented to assist in understanding the results of the sensitivity
41 analysis the 2007 SAB requested. It would also be helpful to see a more quantitative
42 characterization of how the 1974 – 1976 well water re-testing results differed from the
43 results of tests conducted in 1962-64, on which the risk modeling relied. Table B-1
44 indicates the results were “similar”; however, it is not clear how to interpret this.
45

- 1 • **Upper and lower limits in water concentration.** EPA responded to SAB’s request for
2 sensitivity analysis or Monte Carlo analysis with respect to well water concentrations in
3 the villages with more than a single measurement by re-estimating the model using
4 minimum and maximum values of the concentrations for each village. Table 5-10
5 indicates the effect (in terms of estimated cancer incidence) is up to about a $\pm 30\%$
6 change. Although EPA used upper and lower limits, rather than low and high percentile
7 values or Monte Carlo analysis as SAB had suggested, the sensitivity analysis responds
8 adequately to the recommendation. As noted above, however, more information on the
9 variability in the underlying water concentration data is needed to substantiate the reported
10 models and results.
11
- 12 • **Modeling data and parameters.** The SAB suggests that EPA publish the data and
13 parameter tables used in its modeling analysis. As requested by the 2007 SAB report, this
14 would strengthen the scientific credibility and transparency in the assessment.
15
- 16 • **Selection of a reference population.** EPA has tested the sensitivity of the risk model with
17 respect to the choice of reference population (southwest Taiwan, all Taiwan, or no
18 reference population) and to the value of non-water arsenic intake (i.e., in accordance with
19 EPA’s document, this refers to food intake) for both reference and exposed populations.
20 Results indicate that the cancer incidence risks are fairly robust, with the exception of
21 female bladder cancer risks. The sensitivity displayed for female bladder cancer risks
22 seems to warrant further explanation – the result is described but not explained in the
23 accompanying text (pp. 141-2). Additionally, EPA might consider whether any
24 combinations of these parameter variations should be examined – e.g., using different non-
25 water intake values in combination with a different reference population.
26

27 The SAB notes that there is tremendous interest in the risk associated with consumption of
28 water that is contaminated with inorganic arsenic and suggests that EPA discuss how their results
29 should be interpreted in light of existing population-level data on bladder and lung cancer risk for
30 exposure levels that are relevant for U.S. populations. The idea of providing a “reality check” on
31 the estimated risk levels was discussed. The SAB recognizes that IRIS toxicological reviews are
32 not intended to provide a complete risk assessment but rather a summary and synthesis of the
33 toxicological evidence that supports risk assessment. Hence, an estimation of risk attributable to
34 arsenic in drinking water in U.S. populations versus the observed incidence of cancer is not
35 appropriate within the purview of this document. The SAB considers this as a difficult but
36 important exercise and recognizes that this is probably better suited for inclusion in other risk
37 assessment and characterization documents developed by the agency.
38

39 **Charge Question 3:**

40
41 *The SAB did not recommend specific values for the exposure assumptions or parameters*
42 *used in the cancer model. They did, however, recommended evaluating the impact on the cancer*
43 *risk of using a range of values, assessing the variability, and conducting a sensitivity analysis for*
44 *exposure parameters (e.g., water intake, background dietary exposure).*
45

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

6
7 **Please comment on EPA’s sensitivity analyses and choice of the exposure assumptions used**
8 **in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.**

9 Response:

10
11 The 1999 NRC noted that assessment of arsenic exposure via drinking water is often
12 based on the measurements of arsenic concentrations in drinking water and assumptions regarding
13 the amount of water consumed. Such data are estimates, the uncertainty of which will depend on
14 the method used. The 2001 NRC added that the method used to characterize arsenic dose in a
15 study is a source of uncertainty in arsenic dose-response assessment. Furthermore, the NRC noted
16 that the choice of the dose measurement affects the interpretation of an epidemiological study and
17 the choice of the dose-response model.

18
19 The 2007 SAB agreed that water consumption (via drinking as water, in beverages, or in
20 cooking water) assumptions have a substantial impact on the assessment of arsenic’s risk.
21 However, the 2007 SAB did not recommend specific values for EPA to use in evaluating dose-
22 response in the Taiwanese study nor for levels of exposure in the U.S. population risk estimates. It
23 did recommend that uncertainty in this parameter be evaluated for both the Taiwanese study
24 population and the U.S. populations at risk. The 2007 SAB recommended that EPA should:

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

35
36 The NRC (2001) recommended that EPA consider the background dietary intake of
37 inorganic arsenic and incorporate the adjustment values of 0, 10, 30, and 50 µg per day into the
38 cancer risk calculations. The 2007 SAB also agreed that arsenic levels in food are important
39 considerations for EPA’s assessment of lung and bladder cancer risk associated with exposures to
40 arsenic in drinking water. However, the 2007 SAB once again did not recommend a specific
41 value for EPA to use in its base risk assessment. It did recommend a range of values for
42 consideration by EPA in its sensitivity analysis and the 2007 SAB offered suggestions to EPA for
43 additional analytical steps to clarify the impact of food levels of arsenic on dose-response and
44 exposure as it revises its risk estimates. The 2007 SAB recommended that EPA should: 1)
45 Conduct sensitivity analyses using a range of total arsenic food intake values from at least 50 to

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

7
8 The SAB finds EPA's revisions to the IRIS assessment to be partially responsive to the
9 2007 SAB recommendations regarding the sensitivity analyses and choice of the exposure
10 assumptions used in modeling cancer risk. The SAB provides two primary general suggestions
11 for improving the responsiveness of the assessment. They include, making more transparent the
12 scientific basis of the exposure assumptions used; and enhancing the rigor and transparency of the
13 sensitivity analysis.

14
15 The basic approach to the sensitivity analysis is adequate for meeting the minimum
16 requirements for the intended purpose, and is responsive to the 2007 SAB recommendation in that
17 the impact of choice of assumptions is shown in terms of specific cancer risks (lung and bladder,
18 males and females). In evaluating the consequences of choices regarding modeling assumptions
19 and intake values, the IRIS assessment states, "The agency felt that the currently available data
20 were insufficient to support detailed probabilistic uncertainty and variability estimation." The
21 SAB agrees with this conclusion. There are sufficient data to support development of variability
22 and/or uncertainty distributions for some inputs, such as drinking water consumption rates in the
23 United States, but the data are not available to assign corresponding distributions for the
24 Taiwanese populations.

25
26 The SAB notes that much of the documentation addressing the scientific basis of the
27 exposure assumptions was available through separate documents (e.g. EPA Issues Paper) that if
28 incorporated within the current assessment, will help address the SAB's concerns. The SAB
29 recommends that relevant information from these documents be integrated within the current
30 document as appropriate with the goal of enhancing transparency and scientific credibility.

31
32 The SAB is providing the following specific suggestions for making the scientific basis of
33 the exposure assumptions used more transparent and enhancing the rigor and transparency of the
34 sensitivity analysis.

- 35
- 36 • **Better explanation of what the sensitivity analysis shows.** The sensitivity analyses
37 presented offer insight as to how the cancer potency estimates change as drinking water
38 consumption and non-water arsenic intake assumptions change. The various non-water
39 arsenic intake rate assumptions produced modest changes in risk, with the exception of
40 bladder cancer risk in females. This calculated risk was very sensitive to the non-water
41 intake rate assumption. The assessment and this analysis will be strengthened by
42 providing a short explanation for why this is the case.
 - 43
44 • **Need for better justified default assumptions.** Despite some effort to discuss drinking
45 water consumption rates and sources of information for non-water arsenic intake rates, the
46 reasons for some of the specific values chosen to be included in the sensitivity analyses

1 are not clearly justified. For example, the “default” drinking water consumption rate for
2 Taiwanese males is 3.5 L/day, citing precedent from U.S. EPA (1988), Chen et al. (1992),
3 and NRC (1999 and 2001). For the sensitivity analysis, alternative values of 2.75, 3.0, and
4 5.1 L/day were evaluated [along with alternative values for Taiwanese females]. No
5 rationale is provided for these specific numbers, other than they are thought by the agency
6 to span a “reasonable range of values” (see page A-6). To enhance transparency in this
7 example, it would be helpful to know the scientific basis for selecting the lowest and
8 highest numbers (defining the range). Also, if the intent was to illustrate effects at the
9 boundaries of the range of drinking water consumption rates, it is unclear why the lowest
10 estimate for males (2.75 L/day) was not consistent with the lowest estimate for females
11 (2.0 L/day) (see Table 5-10), especially given the SAB’s request to justify different
12 consumption values for men and women. Furthermore, no values for drinking water
13 consumption rates for Taiwanese women were evaluated below the “default” rate of 2.0
14 L/day, suggesting that the value selected by the agency is at the limit of the range of
15 reasonable values for this parameter. The effects on risk were determined based on
16 assumptions that both the reference and exposed populations had non-water intake rates of
17 0, 30, and 50 µg/day arsenic. Although compliant with SAB’s 2007 recommendations,
18 better discussion of dietary intake of inorganic arsenic would help the reader understand
19 whether the various values included in the analysis represent different interpretations of
20 the existing data, bounding estimates, or something else.

- 21
- 22 • **Consider additional permutations of gender-specific water consumption.** The 2007
23 SAB recommended: “Because data on gender differences in consumption in Taiwan are
24 limited, a better justification for assuming different consumption levels by gender is
25 needed, particularly given the lack of sex difference in consumption in United States and
26 observed in studies from other countries (Watanabe et al., 2004). In the absence of such a
27 justification, the SAB recommends an additional sensitivity analysis to examine the
28 impact of equalizing the gender-specific consumption level.” The agency complied with
29 this recommendation to some extent, evaluating the effect on risk of setting the drinking
30 water consumption rate for both Taiwanese males and females at 2.75 L/day in the
31 sensitivity analysis. However, the basis for the choice of this particular drinking water
32 consumption rate is not explained. Also, by examining a single drinking water
33 consumption rate for both sexes, the influence of selection of different rates on resulting
34 risk is not illustrated. In order to be responsive to the 2007 SAB recommendation,
35 discussion of the impact of using a single drinking water consumption rate for males and
36 females for the Taiwanese populations needs to be justified and expanded.
 - 37
 - 38 • **Need to clearly delineate the basis for water concentration assumptions.** Based on the
39 data in tables 5-10 and 5-11, it isn’t clear if EPA has completed the calculations that the
40 SAB requested. Those tables noted that the sensitivity analyses used minimum and
41 maximum village water arsenic concentration values. It isn’t clear if only the villages
42 with more than one well measurement were used or if all the villages were used. EPA
43 needs to clarify the water concentration assumptions. This recommendation is also
44 consistent with recommendations under charge question #2.
 - 45

- 1 • **Need to address water consumption rates of susceptible groups.** The 2007 SAB
2 recommended that the “EPA should evaluate the impact of drinking water consumption
3 rates associated with more highly exposed population groups with potentially different
4 exposures and susceptibilities (e.g. children, pregnant women) in its arsenic exposure
5 estimates as the agency determines the overall effects of drinking water consumption rates
6 on arsenic risk.” In the current 2010 draft IRIS assessment, the impact of drinking water
7 consumption rates associated with more highly exposed population groups with
8 potentially different exposures and susceptibilities (e.g. children, pregnant women) in its
9 arsenic exposure estimates has not been evaluated. During the April meeting, the agency
10 indicated that including these populations in the sensitivity analysis would be difficult and
11 of limited value. So that the response to this 2007 SAB comment is clear, an explanation
12 of why this aspect of the sensitivity analysis was not conducted should be included in
13 Appendix A.
14
- 15 • **More complete and graphical analysis.** EPA has responded to the 2007 SAB’s
16 suggested sensitivity analysis with the development of Tables 5-10 and 11 along with
17 Figure 5-2 showing the influence of various exposure assumptions including water arsenic
18 concentration, non-water arsenic intake, and water consumption on various cancer
19 endpoint risks. The tables and figure are efficient in providing a “snapshot” of their
20 influence for various assumed point estimates; however, a more complete description of
21 their influence can be shown by graphing across the range of plausible values.
22 Admittedly, the graphical representation will be less efficient (i.e., require more space) but
23 will provide a more complete depiction. To the extent possible, it would be useful to
24 illustrate on these graphs the various historically and currently “assumed” values.
25
- 26 • **Testing the effects of layered assumptions.** To further respond to the 2007 SAB’s
27 recommendation, EPA tested the effects of changing assumptions one at a time. This
28 approach is necessary to clearly show how individual values potentially affect cancer
29 potency and risk. This approach does not, however, indicate how changes in assumptions
30 might interact to produce overall changes in potency and risk. Testing all of the various
31 permutations of changes in assumptions in a sensitivity analysis would be arduous and of
32 dubious value. Nevertheless, it may be instructive to examine selected sets of exposure
33 assumptions and their effect on cancer potency. This would provide an indication of the
34 extent to which a reasonable range of exposure assumptions in the aggregate has the
35 potential to affect cancer potency estimation.
36
- 37 • **Clarification of what the exposure assumptions are intended to represent.** It is often
38 unclear in the assessment whether the exposure assumptions (e.g., drinking water
39 consumption rate) selected are intended to represent best estimates of the mean for the
40 exposed population, upper confidence estimates of the mean, upper percentile values,
41 upper confidence limit estimates of an upper percentile value, or something else. This
42 should be specified in the IRIS assessment. During the April meeting, the agency
43 indicated that different types of assumptions may be appropriate for different values. The
44 rationale for why a particular value is used should be provided in the IRIS assessment. For
45 example, why an upper percentile drinking water ingestion rate is appropriate for the U.S.

1 population while an average (or upper bound average) assumption is used for the
2 Taiwanese population.
3

- 4 • **The bases for the exposure assumptions selected are not adequately described.** The
5 SAB in 2007 stated, “Much greater rigor needs to be applied in discussing and presenting
6 documented data sources and making clear the basis on which assumptions are being
7 made and the relative strength of those assumptions.” That criticism applies to the 2010
8 version of the IRIS assessment as well. Some examples include:
9
 - 10 ○ For non-water arsenic intake, EPA has selected an assumed intake value of 10 µg /day.
11 Discussion in support of this selection occurs on pg. 123-124 of the revised assessment
12 and is based on six references including US EPA 1989, Schoof et al. 1998, Yost et al.
13 1998, NRC 1999, NRC 2001, and EPA 2005c. Of these, there are only two references
14 that relate to the peer-reviewed primary literature, reflecting the scarcity of data from
15 which to base this estimate. Although EPA does a reasonable job of discussing these
16 reports, the current assessment lacks a specific rationale or justification for the selected
17 value. It appears that the US EPA 1989 reference supporting an intake range of 2
18 µg/day to 16 µg/day may provide the rationale for this selection. Since this reference
19 is not easily available, the SAB recommends that within the IRIS assessment a more
20 complete discussion of data and evidence supporting this intake range be provided in a
21 manner similar to what has been provided for Schoof et al. 1998 and Yost et al. 1998.
22 In the current assessment, it is unclear what the 2 to 16 µg/day estimate is based on.
23 Moreover, the current assessment does not provide a specific justification or rationale
24 for this selection, but rather makes a broad statement “Based on available information,
25 EPA selected 10 µg /day as the best estimate for non-water arsenic intake (food
26 sources) in baseline calculations.” The selection of this value can be strengthened by:
27 1) elaborating on the lack of data or evidence upon which to base this estimate; 2)
28 distinguishing between evidence that is primary (i.e., peer-reviewed with data
29 collection) and reports that provide expert assessment, and 3) providing specific and
30 scientific justification for the selected value that can be traced to the primary literature.
31 Again, because of the effect this parameter has on the risk estimates, providing support
32 for the values chosen for this parameter is important.
33
 - 34 ○ The current dose-response assessment is based on an assumed water intake value of
35 3.5 and 2.0 L/day for men and women, respectively. As with the assumed values for
36 non-water intake above, justification for these values can be strengthened by
37 establishing a clear link to data within the primary literature where possible. The
38 specific relevant findings from Chen et al. 1992 and Chowdhury et al. 2001 should be
39 provided in relation to the selected values. In the current assessment, it appears that
40 EPA justified the selected values largely based on precedent (e.g., EPA and NRC
41 reports) rather than on the data reported in the primary literature. It is unclear why
42 EPA did not base their estimate on the data of Chowdhury et al. 2001 since it is unique
43 and relevant. No discussion is provided of the data available from Chen et al. 1992.
44 To the extent that EPA relies on previous EPA and NRC assessments, the link to the
45 primary data (if available) should be maintained. The problem illustrated by the 2010

1 assessment is that these assumed values take on a life of their own and the evidence
2 upon which they are based is lost.
3

- 4 • **The reason for limiting non-water intake to dietary sources is not explained.** Non-
5 water exposure is currently assumed to consist entirely of arsenic in the diet. For
6 completeness and transparency, EPA should provide a short description of alternate routes
7 of exposure (e.g. inhalation, non-dietary ingestion, dermal absorption) from other media
8 such as soil and include arsenic intake estimates using EPA's routine exposure
9 assumptions for both the Taiwan and the U.S. populations; EPA should provide
10 justification for why these other exposures were not considered in the current dose-
11 response assessment. If the reason is that other pathways are assumed to be minor relative
12 to arsenic intake from diet, some illustration of this should be provided as justification.
13

14 **Other Comments**

- 15
- 16 • **More clear delineation of organic vs. inorganic exposure assumptions.** It would be
17 helpful to provide a paragraph for IRIS users explaining why the organic arsenic
18 compounds do not affect the risk estimates for inorganic arsenic. The explanation will
19 probably be fairly straight forward for the seafood organic arsenic compounds. This may
20 not be as straight forward for any organic arsenic compound in produce (e.g. rice, etc.).
21 As a related comment, when discussing non-water arsenic intake care should be taken to
22 distinguish between inorganic and organic or total arsenic in food. The current draft
23 assessment is in some places ambiguous, referring simply to “arsenic.” (see pages 123-
24 124).
25
- 26 • **Value in identifying research gaps.** Given the importance and scarcity of data for
27 purposes of estimating exposure, the SAB suggests that EPA provide a short paragraph
28 describing the research needs along with suggested designs to produce credible estimates
29 for water and non-water intake rates. The research needs are not only to provide point
30 estimates, but data for distribution analysis to support the more credible stochastic
31 approaches to risk estimation. Maybe 10 years from now we will not find ourselves in the
32 position that we are in now of relying on largely the same sparse/inadequate data for risk
33 estimation that we were 10 years ago.
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REFERENCES

Chen, C-J; Chen, C-W; Wu, M-M; Kuo, T-L. (1992) Cancer potential in liver, lung, bladder, and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* 66(5):888–892.

Chen, C-J; Kuo, T-L; Wu, M-M. (1988a) Arsenic and cancers. *Lancet*: letter to the editor. February 20, 1988.

Chowdhury, UK; Rahman, MM; Mondal, BK; et al. (2001) Groundwater arsenic contamination and human suffering in West Bengal – India and Bangladesh. *Environ Sci* 8(5):393–415.

Lash, Fox, and Fink (2009) *Applying Quantitative Bias Analysis to Epidemiological Data*, Springer.

NRC (National Research Council). (1999) Arsenic in drinking water. National Academy Press, Washington, DC. Available online at <http://www.nap.edu/openbook/0309063337/html/R1.html>.

NRC (National Research Council). (2001) Arsenic in drinking water (2001 update). National Academy Press, Washington, DC. Available online at <http://www.nap.edu/openbook/0309076293/html/R1.html>.

Schoof, RA; Yost, LJ; Crecelius, C; et al. (1998) Dietary arsenic intake in Taiwanese districts with elevated arsenic in drinking water. *Hum Ecol Risk Assess* 4:117–135.

U.S. EPA SAB (2007) Advisory on EPA’s Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: A Report of the US EPA Science Advisory Board. (EPA-SAB-07-008) Available online at [http://yosemite.epa.gov/sab/sabproduct.nsf/EADABBF40DED2A0885257308006741EF/\\$File/sab-07-008.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/EADABBF40DED2A0885257308006741EF/$File/sab-07-008.pdf)

U.S. EPA (2005a) Draft Science Issue Paper: Mode-of-action for Cacodylic Acid (Dimethylarsinic Acid) and Recommendations for Dose Response Extrapolation Office of Pesticide Programs. Available online at: http://www.epa.gov/pesticides/reregistration/cacodylic_acid/dma_moa.pdf

U.S. EPA (2005b) 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) Office of Research and Development. Available online as Appendix E at: http://www.epa.gov/pesticides/reregistration/cacodylic_acid/dma_moa.pdf

U.S. EPA (2005c) Draft Toxicological Review of Ingested Inorganic Arsenic. Office of Water. Available online at: http://water.epa.gov/scitech/swguidance/waterquality/standards/criteria/aqlife/pollutants/arsenic/upload/2007_07_12_criteria_arsenic_sab_AsDraft_SAB.pdf

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This report does not represent EPA policy

1 U.S. EPA (2005d). Issue paper: inorganic arsenic cancer slope factor. Arsenic Cancer Slope
2 Factor Workshop. Available online at
3 http://water.epa.gov/scitech/swguidance/waterquality/standards/upload/2007_07_12_criteria_arsenic_sab_ASIssues_SAB.pdf
4
5
6 U.S. EPA (1989) Report on Arsenic (As) Work Group meetings. Memorandum. From:
7 Abernathy, CO; Marcus, W; Office of Drinking Water; and Chen, C; Gibb, H; White, P; Office of
8 Research and Development; to Cook, P; Office of Drinking Water; and Preuss, P; Office of
9 Regulatory Support and Scientific Management. February 23.
10
11 Wu, MM; Kuo, TL; Hwang, YH; Chen CJ. (1989) Dose-response relation between arsenic
12 concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol
13 130:1123–1132.
14
15 Watanabe C; Kawata A; Sudo N; Sekiyama M; Inaoka T; Bae M; Ohtsuka R. (2004) Water
16 intake in an Asian population living in arsenic-contaminated area. Toxicol Appl Pharmacol.
17 198(3):272-82. Review.
18
19 Yost, LJ; Schoof, RA; Aucoin, R. (1998) Intake of inorganic arsenic in the North American diet.
20 Hum Ecol Risk Assess 4:137–152.
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1 **Appendix A - Minor edits**
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- 4 • Pages 139 and 140: Providing some information in these tables about the range in village
5 water arsenic concentrations would be useful.
6
- 7 • Type in footnote for Table 5-11. Table 5-8 should probably be Table 5-10.
8
- 9 • Page 141, line 27. Tables 5-6 and 5-9 should be Tables 5-10 and 5-11
10
- 11 • Page 142 – line 3. Should both increased and decreased be there?
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