March 29, 2010

Dr. Sue Shallal
Designated Federal Officer (DFO)
EPA Science Advisory Board (1400F)
1200 Pennsylvania Avenue, NW.
Washington, DC 20460

Re: Comments on the draft "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)"

Dear Dr. Shallal,

On behalf of the undersigned, we are providing these comments to be considered by the Arsenic Work Group during its meeting on April 6-7, 2010. There are numerous issues which the work group must address in its review, not all of which are encompassed by the charge questions presented by EPA. We believe that this Work Group should consider whether EPA has fully addressed all the issues and advice in the 2007 Advisory Report from the Scientific Advisory Board and has provided the Work Group and the public at large with a scientifically rigorous, defensible, and transparent assessment.

Review of the 2007 Advisory Report from the SAB identifies several critical areas that EPA needed to address. These include, in brief:

- development of a physiologically based pharmacokinetic model for inorganic arsenic in order to better understand the metabolism of arsenic, regardless of it source
- identification of the shape of the dose-response curve at low exposures using additional mechanistic and epidemiological reseach, to support the likelihood of a threshold based on the lack of direct genotoxicity and available mechanistic data
- evaluation of all the epidemiological studies, judging all by the same, transparent criteria, giving consideration to the uncertainties of exposure analysis, and further that low dose studies should be separately considered including through use of integrated analyses
- consideration of nonlinear forms of the dose-response relationship, given that all experimental evidence on mode of action support a nonlinear dose response at low exposure levels, even though information at that time was insufficient for the Panel to recommend a specific nonlinear form.
- evaluation of a range of values related to food and water intake, including sensitivity analyses of the impact of using ranges, and clear justification for any conclusions regarding differences based on gender

Because of the limited time available to review a 575 page highly technical document, we have focused our comments on the areas of evaluation of the epidemiological data and its appropriate analysis and have attached detailed comments on those areas. We refer the work group to comments submitted by others on the remaining critical areas.

Recognizing that the purpose of IRIS assessments is to support regulatory actions of EPA, the draft assessment for inorganic arsenic must be evaluated in relation to the highest quality science but also to its reliability and utility to the Agency for decision making. We urge the work group to fully evaluate the draft assessment to ensure that meaningful and reliable information is available for the Agency's regulatory activities. We believe that the current assessment, with a proposed cancer risk factor of 25.7, is not scientifically justifiable and will lead to a complete inability of Agency risk managers to make any kind of a meaningful decisions.

Respectfully submitted,

Rio Tinto Limited
William J. Adams, Ph.D.
Chief Adviser, Health, Safety and Environment
4700 Daybreak Parkway
South Jordan, UT 84095

Wood Preservative Science Council
c/o Elizabeth Brown, Ph.D.
Steptoe & Johnson, LLP
1330 Connecticut Ave NW
Washington, DC 20036

Technical Memorandum

Comments on U.S. EPA Draft Toxicological Review of Inorganic Arsenic

Prepared for

Wood Preservatives Sciences Council
and
Rio Tinto

Prepared by

Exponent
15375 SE 30th Place, Suite 250
Bellevue, WA 98007

with

Pamela Mink
Emory University
Atlanta, GA

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Comments on U.S. EPA Draft Toxicological Review of Inorganic Arsenic

This report comments on the U.S. EPA draft Toxicological Review of Inorganic Arsenic, dated February 2010, which supports summary information on the Integrated Risk Information System (IRIS). Comments are presented in accordance with responses to the U.S. EPA Charge Questions to the 2010 Science Advisory Board (SAB), particularly certain aspects of Charge Questions 1 and 2 concerning epidemiological studies and the dose-response relationship at low doses, respectively. We also comment briefly in the summary on Charge Question 3 (inorganic arsenic in diet and water intake) which is covered in other comments being submitted to the SAB. These charge questions request comment on EPA's compliance with the recommendations of the 2007 SAB. Although the Charge to the 2007 SAB was broader in scope, it also largely constrained the focus of the panel regarding inorganic arsenic to commenting on EPA's implementation of a dose-response assessment based primarily on the work of NRC (2001). Because of the wealth of new scientific data since the NRC's evaluation, our comments are also based on other scientific information available to inform risk assessments of inorganic arsenic.

1.0 Summary of Comments

Overall, the dose-response assessment presented in the draft IRIS document (U.S. EPA 2010b) is based primarily on the work of Morales et al. (2000) and NRC (1999; 2001) and is largely uninformed by the past 10 years of additional epidemiological studies and mechanistic research on the toxicology and mode of action of arsenic. The proposed assessment used studies on the arseniasis endemic area of Southwest Taiwan (Wu 1989; Chen et al. 1988; 1992), which examined bladder and lung cancer rather than skin cancer. Skin cancer had been examined earlier for this area as part of EPA's 1988 assessment (U.S. EPA 1998). Although the proposed assessment used more sophisticated modeling techniques than in 1988, the general approach is the same in that the proposed cancer slope factor (CSF) represents a linear extrapolation from cancer risks at high doses for the Southwest Taiwanese population, which largely ignores the shape of the dose-response relationship at lower doses (e.g., <150 μg/L, ppb of arsenic in drinking water) even within this population. Consequently, it is not surprising that the proposed CSF will result in predicted risks for background exposures to inorganic arsenic in soil, water, and food (Tsuji et al. 2007) that will be well in excess of the upper end of EPA's target risk range of 1 in 10,000. Although this result is not a concern of the draft IRIS document, it does indicate the consequences of an overly conservative approach.

The findings from our review are as follows:

- The evaluation and selection of epidemiological studies was inconsistent and was not conducted using clearly defined *a priori* and transparent criteria. What constituted a significant weakness or strength was not presented. It is also unclear why a single study had to be selected rather than evaluating the weight of evidence from multiple studies.

Justification for the exclusion of each study within the context of the criteria-based review was not provided.

- Exposure misclassification and small study size or low power appear to be primary reasons that all studies other than those of Southwest Taiwan (i.e., mainly the high dose region of these data) were excluded from consideration, yet the effect of exposure misclassification has been incorrectly interpreted and the evaluation of power was inconsistent and did not take into consideration the direction or precision of the relative risk estimates (particularly in low exposure categories), or weight and consistency of evidence at low doses from multiple studies, including Southwest Taiwan. Limited statistical power does not necessarily preclude the detection of statistically significant associations. Consistency and precision of estimated relative risks from the "low exposure" studies, when analyzed individually or as a meta-analysis, are more informative than a simple *post-hoc* power calculation.

- The dose-response evaluation presented is not reconciled with the already substantial and growing database from other studies. Several new epidemiological studies are also available that were not considered by the draft IRIS document. These studies show consistency with earlier findings of a lack of increased risk at low doses. The two recent studies from Northeast Taiwan (Chen et al. 2009, 2010) address many of the weaknesses identified by EPA as limiting the previous analysis of bladder cancer in this cohort (Chiou et al. 2001), including length of follow-up time and accuracy of the source of cancer diagnoses). The recent studies that examine smoking do not show evidence of an interaction between arsenic and smoking affecting cancer risk.

- Meta-analysis of previous and new studies on the association of low dose arsenic exposure with bladder cancer indicates consistent, statistically stable, and robust estimates of relative risks that are below 1.0 (i.e., pattern of decreasing bladder cancer risk with increasing arsenic exposure) for non-smokers. Presumed bias toward the null as a result of nondifferential exposure misclassification and low statistical power thus does not explain the consistent, although generally not significant, ***inverse association*** observed in low dose studies of non-smokers.

- The epidemiological data at low doses in Southwest Taiwan and in other studies consistently reflect a sublinear dose-response relationship or threshold for significant risk below an arsenic concentration in water around 100 to 200 μg/L.

- The linear dose-response relationship assumed by the draft IRIS document essentially ignores the low dose data, particularly when a comparison or reference population is used to anchor the lower end of the dose-response relationship. The "large" database used for this population is thus mostly at high doses, well above exposures that would be assessed by most risk assessments of environmental arsenic in the United States. The estimates are statistically stable because of the large numbers of data at high doses with elevated risk combined with the Poisson linear model. Such statistical stability should not be confused with accuracy or representativeness in depicting the actual relationship at low doses.

- The comparison population used to anchor risks at low doses is not an appropriate comparison, without including a factor for area in the model (e.g., arseniasis endemic area versus the "Southwest Taiwan" region). As recognized in previous evaluations by EPA (66 Fed. Reg. 6976–7066) and NRC (2001), cancer risks in the Southwest Taiwanese study population are more elevated than those in the comparison population even at similar arsenic water concentrations (water concentration for comparison group was assumed to be zero but was likely the same as many of the low dose villages). Thus, some factor other than arsenic appears to be elevating cancer risks in the arsenic exposed villages considered.

- The sensitivity analysis conducted by the draft IRIS document evaluated the effect of using or not using the comparison population, but used the full range of the arsenic exposure data and the linear model. Thus, the changes presented without the comparison population are constrained and would be even greater (e.g., than the 88 percent decrease presented for female bladder cancer) if, for example, the effect were examined for only the low dose data (e.g., <150 ppb) or if non-linear modeling were used.

- In addition to the epidemiological studies, the growing weight of evidence on the mode of action for carcinogenesis of inorganic arsenic continues to indicate mechanisms that would be associated with thresholds for significant risk. The EPA 2005 cancer risk guidelines allow for the consideration of nonlinear dose response relationships for chemicals that are not direct mutagens and permit reliance on the toxicological weight of evidence even when some uncertainty is present. Detailed comments on mode of action are described in other comment submissions (e.g., Gradient, Sam Cohen) and are not discussed in this report.

- Other factors that contributed overestimated risks for inorganic arsenic are assumptions on dietary intake of inorganic arsenic and the water intake in Taiwan. Specifically, the draft IRIS document underestimates the amount of inorganic arsenic intake in the diet for the Southwest Taiwanese population relative to the United States. The document also underestimates that amount of water consumption in the Southwest Taiwanese population. These assumptions underestimate the amount of arsenic exposure and thereby make risks appear higher per arsenic dose (i.e., increase the CSF). Detailed comments regarding this issue are being provided by Environ.

2.0 Charge Question 1: Evaluation and Selection of Epidemiological Studies

In Charge 1, EPA has asked the current SAB to comment on their response to the 2007 SAB's recommendations regarding the evaluation of the epidemiological literature. EPA states that they have performed "an extensive review and evaluation of all available human studies for iAs using the criteria suggested by the SAB" (U.S. EPA 2010a). Furthermore, EPA states that they agree with the 2007 SAB conclusion "that the Taiwanese data were the best available for determining the carcinogenic risk due to exposure to iAs" and that "there were no other

additional epidemiological studies that had comparable utility to the Taiwanese dataset (Wu 1989; Chen et al. 1988; 1992)" (U.S. EPA 2010a).

The specific recommendations from the SAB (2007) included the following:

> *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.* (Executive Summary, p. 7, emphasis added)
>
> *All of these studies, including those from Taiwan, Chile, Argentina and the U.S. as described above, should be judged by the same set of criteria, with the comparative assessment of those criteria across studies clearly laid out in a tabular format. Some of the criteria have been listed in the previous paragraph.* ***The relative strengths and weaknesses of each study need to be described in relation to each criterion.*** *The caveats and assumptions used should be presented so that they are apparent to anyone who uses these data. Included in the risk assessment background document should be a complete and transparent treatment of variability within and among studies and how it affects risk estimates.* ***The present lack of transparency in the application of the criteria in the process of study selection was pointed out by several panel members.*** (p. 39, emphasis added)

2.1 Lack of Transparency of Selection Criteria and Study Selection

In the current draft IRIS document (U.S. EPA 2010b), epidemiologic studies are presented in both a narrative and tabular format. As stated in this document, "Each publication was evaluated using a uniform set of criteria, including the study type, the size of the study population and control population, and the relative strengths and weaknesses of the study" (U.S. EPA 2010b). **Nevertheless, the application of the criteria in the process of study selection, and particularly in the process of study elimination, was not transparent.** Furthermore, it was not stated *a priori* what features would be required for a study to be "of potential utility." As currently written, the reader is unable to replicate the process undertaken by EPA not only to reach the same conclusion but also to be able to explain and justify the decision reached for each study considered. It is not necessary for the reader to agree with the final decision, but he/she must be able to understand the rationale and justification used by EPA. Selected examples of lack of explanation and transparency in the draft IRIS document follow:

- **Data from studies are presented inconsistently.** In the study listed as "Chen et al., 1988b", (see tables in Appendix B of U.S. EPA 2010b) EPA lists the number of cases and controls for the nested case-control study (241 cases, 759 controls), but provide SMRs from the cohort study, which was based on fewer cases (e.g., 15 bladder cancer deaths, 7 skin cancer deaths, 28 lung cancer deaths, 17 liver cancer deaths, 4 colon cancer deaths).
- **Sample size is listed for each study, but adequate sample size or study power is not stated *a priori*, nor is study size mentioned consistently as a strength or weakness, even for studies of similar size.** For example, "small size of study population" is listed as a weakness for the case-control study by "Bates et al., 1995" (71 bladder cancer cases, 160 controls; see tables in Appendix B of U.S. EPA 2010b) but is not listed as either a strength or weakness for the case-cohort study by "Kurttio et al., 1999" (61 bladder cancer cases, 49 kidney cancer cases, 275 referents; relative risks presented for bladder cancer; Appendix B of U.S. EPA 2010b). Given that these studies have similar numbers of bladder cancer cases, it does not appear that the same criteria were applied. Further explanation is required. Furthermore, despite the "small size of study population" in the Bates et al. (1995) study, ***statistically significant inverse associations were observed*** for analyses of Exposure Index 2 restricted to Never Smokers, specifically for exposure categories between 33 and 74 mg/L x years. In addition, adequate sample size to achieve a given level of statistical power will vary considerably depending on the study design (e.g., case-control studies will tend to be more efficient for rare diseases and require fewer subjects than prospective cohort studies or ecological studies such as those conducted in Southwest Taiwan).
- **Potential confounding and unmeasured confounders are not discussed in a systematic manner**. It would be helpful to readers (including risk managers) if a discussion of confounding and important confounders were included. For example, for an exposure to be a confounder, it would need to be associated with the exposure (arsenic in drinking water), the outcome (site-specific or all-cause cancer), and not be an intermediate on the causal pathway. For the discussion of uncontrolled or residual confounding to be both meaningful and transparent, the draft IRIS document should discuss what factors (if any) would need to be controlled in analyses of arsenic in drinking water and specific cancer endpoints. It is not clear why lack of adjustment for occupation is listed as a weakness in some studies (e.g., Marshall et al. 2007; Knobeloch et al. 2006), why adjustment for occupation is listed as a strength in some studies (e.g., Bates et al. 1995; Steinmaus et al. 2003), and why adjustment for occupation is not mentioned at all in others (e.g., Lewis et al. 1999; Karagas et al. 2001; all studies cited in Appendix B of U.S. EPA 2010b). In other words, the criteria for evaluation of confounding by occupation (or any factor) are not specified.
- **Some of the weaknesses listed appear to be incorrect.** For example, in the evaluation of the study by Chiou et al. (2001), the IRIS document states, "Weaknesses include possible diagnostic bias as the result of medical data collection from various community hospitals and recall bias from self-reported information." While it is true that any epidemiologic study may suffer from misclassification, "recall bias" is a type of systematic error that is typically encountered in case-control studies, not in cohort

studies such as Chiou et al. (2001). One of the advantages of cohort studies is that information on exposure and potential confounding factors is ascertained PRIOR TO the onset of disease, thus avoiding the likelihood of recall bias. Thus, it is not clear why recall is listed as a weakness for this cohort study.

2.2 Misinterpretation of Epidemiological Concepts: Exposure Misclassification and Study Power

In addition to the above issues, there are several instances where epidemiologic concepts are discussed incompletely or inaccurately. Two such instances (exposure misclassification and sample size or study power) appear to constitute the major rationale for discounting the many low dose studies in the United States and other countries and selecting Southwest Taiwan as the best study for basing estimates of cancer risk at lower doses examined by risk assessments of arsenic. The draft IRIS document states that exposure misclassification may result in an apparent lack of statistical significance of a positive dose-response relationship at low doses, particularly for populations in the United States who are more mobile than in Taiwan. The document also notes that many studies lack the sample size and hence study power of the Southwest Taiwanese database. These types of assertions incorrectly interpret or apply epidemiological concepts and hence are inaccurate.

2.2.1 Exposure Misclassification

Nondifferential misclassification does not always produce bias in the direction of the null (i.e., relative risk of 1.0). There are certain conditions under which the direction of bias is predictable, but these conditions are not met in the epidemiologic studies of health effects of arsenic in drinking water. This concept is explained in relatively simple terms in Rothman's textbook, *Epidemiology: An Introduction* (2002):

> *Nondifferential misclassification of a dichotomous exposure will always bias an effect, if there is one, toward the null value.* ***If the exposure <u>is not dichotomous</u>, there may be bias toward the null value; but there may also be bias <u>away from the null value</u>****, depending on the categories to which individuals are misclassified.* (p.101, emphasis added)

The more advanced textbook, *Modern Epidemiology* (3rd Ed.), by Rothman, Greenland, and Lash (2008) notes further that the condition of nondifferentiality (that is, classification of exposure has the identical sensitivity and specificity among cases and noncases, and neither disease nor uncontrolled risk factors result in different accuracy for cases compared to noncases) "may seldom be met exactly" (p. 355). Thus, the following statement in the draft IRIS document (EPA 2010) **is incorrect and misleading**:

> *Therefore, studies with low levels of exposure that are ecological in nature (no individual exposure) are more prone to misclassification, which means they are biased toward the null hypothesis* (pp. 95 and 147).

Specifically, it is not true that being prone to misclassification means being biased toward the null hypothesis. It should be noted that the illustration of bias toward the null in the paper cited in the draft IRIS document, by Cantor and Lubin (2007), is based on a **binary** (i.e., dichotomous) exposure. The epidemiologic studies cited in the draft IRIS document measure arsenic in drinking water on a continuous scale and then, for the vast majority of the studies, create multi-level categorical variables to characterize arsenic exposure. For further information on this issue, the reader is referred to Rothman et al. (2008), Dosemeci et al. (1990), Kristensen (1992), Flegal et al. (1991), Wacholder et al. (1991).

The point here is not to downplay the importance of accurate classification of exposure, but rather to emphasize that the direction of bias associated with misclassification is never certain, and is not always even predictable.

2.2.2 Statistical Power

The draft IRIS document praised or criticized epidemiologic studies for statistical power or study size, but there is limited discussion of these issues or of the arguably more important issue of precision. As one example, the following statement is made regarding findings from the ecologic study by Hinwood et al. (1999):

> *When stratified by exposure category, the* ***SIR for prostate cancer was significant*** *at 1.20 (95% CI: 1.06–1.36) for the high soil/high water category only.* ***This result was likely confounded by misclassification (level of population exposure) and limited by low statistical power***" (p. 62, U.S. EPA 2010b, emphasis added)

The standard incidence ratio (SIR) being cited was statistically significant with a 95% CI of 1.06 to 1.36. The limitations referred to are not fully explained. Increased power would improve precision, but there is no mention of precision. In fact, with the exception of liver cancer, the width of the 95% confidence intervals appear to be similar for each exposure level in Figure 2 (Hinwood et al. 1999). It is interesting to note that the SIRs for the lowest exposure category for "all cancers" and for 4 out of 6 cancer sites shown in the figure are below 1.0 (i.e., in the direction of decreased cancer risk with arsenic exposure). As an additional point, misclassification would tend to result in information bias. Lack of control for a confounding factor would result in confounding. The statement "the result was likely confounded by misclassification" requires further explanation or correction. In addition, although low statistical power is listed as a limitation in the narrative section of the draft IRIS document, the tabular summary of Hinwood et al. (1999) does not provide the study size, nor does it list study size or statistical power as a weakness. Inconsistencies in noting study size as a strength or weakness have already been described above. The important point here is that statistical and epidemiological concepts, particularly those that are used in the evaluation of the epidemiologic studies, require explanation and appropriate application. Otherwise certain criticisms of some of the epidemiologic studies cannot be supported, and the removal of these studies from further consideration has not been justified. As described previously, criteria for consideration of

sample size needs to take into account study design (e.g., case-control versus weaker study designs such as ecological).

Finally, as noted above, despite criticisms about small sample size, statistically significant results were observed in some of the analyses of never smokers who had lived at least 50% of their lifetime (until diagnosis) in study towns in the Bates et al. (1995) study (see Table 3, Bates et al. 1995). Thus, limited statistical power does not always preclude the detection of statistically significant associations. **Consistency and precision of estimated relative risks from the "low exposure" studies, when analyzed individually or as a meta-analysis, is more informative than a simple *post-hoc* power calculation.**

2.3 Overall Inconsistent Presentation of Study Evaluation and Selection

The above examples illustrate that the draft IRIS document is inconsistent in its listing of strengths and/or weaknesses across epidemiologic studies with similar characteristics, nor are the strengths and weaknesses described in the context of criteria, as requested by the SAB (2007). Furthermore, some of the weaknesses listed are based on misinterpretation of epidemiologic concepts.

The most critical issue is that even though the strengths of the Taiwan dataset are listed, evidence is lacking of a deliberative or thoughtful process of consideration of other datasets or of considering the relative strengths/limitations of this dataset with respect to others.

The draft IRIS document states,

> *The Taiwanese database is still the most appropriate source for estimating bladder and lung cancer risk among humans (specifics provided in Section 5) because of: (1) the size and statistical stability of the database relative to other studies; (2) the reliability of the population and mortality counts; (3) the stability of residential patterns; and (4) the inclusion of long-term exposures.*

Nevertheless, the SAB (2007) Panel listed several limitations of the Southwest Taiwan database, including

> *…its ecologic character, lack of smoking information, limited precision of exposure estimates, especially among villages with multiple wells, and the possible issue of compromised nutrition among segments of the exposed population.*

These relative strengths and limitations are not reconciled in the present draft IRIS document. EPA's justification becomes even more unclear when the statement about "the reliability of the population and mortality counts" is contrasted with the comment "limitations of mortality data," which appears in the tabular summary for the study by Wu et al. (1989), one of the studies specifically cited as being among the "most appropriate."

In conclusion, EPA has provided only a partial response to the 2007 SAB's recommendation to perform a critical evaluation of the relevant epidemiologic literature, "using a uniform set of criteria and that the results from these evaluations be transparently documented in EPA's assessment documents" (SAB 2007). The review and evaluation of the epidemiologic literature was conducted without describing a methodological approach, the relative strengths and weaknesses of each study were not described in relation to *a priori* criteria, justification for the final decision regarding each study was not provided, and the process of the evaluation was neither transparent nor reproducible.

2.4 Recommendations

In order to achieve what the 2007 SAB requested, it is recommended that EPA take the following steps and report each step as part of the methods and results of the evaluation of the epidemiology studies:

1. Define and describe a clear methodology for reviewing the relevant literature
2. Identify a set of parameters that will be evaluated (study size, control selection, adjustment for potential confounders, etc.)
3. Identify a set of criteria or considerations that will be evaluated with respect to each parameter (e.g., Were the controls population-based or hospital-based or other? What are potentially important confounding factors?)
4. Consider to what extent limitations or weaknesses constitute "fatal flaws" versus caveats for interpretation
5. Evaluate each study against the same set of parameters and criteria/considerations
6. Summarize findings
7. Use this information to inform decisions about "potential utility" of each study for cancer risk assessment
8. Describe and document the decision for each study.

3.0 Additional Epidemiological Studies for Consideration

The current draft IRIS document (U.S. EPA 2010b) lacks references to the epidemiologic literature published during the past 3 years. There are several important primary articles and two meta-analyses that were not included in the draft IRIS document and should be added.

3.1 Individual Studies

Table 1 lists the main features and results of the primary epidemiologic studies that should be reviewed and considered. In the interest of space, the full results have not been reproduced in this table. This table is not intended to provide a critical evaluation of the studies, but simply to identify and summarize some key features.

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Table 1. Epidemiologic studies of arsenic in drinking water and cancer outcomes not included in draft IRIS document

Reference (Study Location)	Study Design	Study Size	Cancer Site (sites)	Study-Specific Exposure Categories	Relative Risk Estimate (95% CI)	Comments
Bladder/Urinary Cancer						
Meliker et al. 2010 (Michigan, US)	Case-Control	411 bladder cancer cases 566 pop. controls	Bladder cancer	As concentration in water (TWA):		From Discussion: "This case-control study included a detailed lifetime exposure assessment and had good statistical power to investigate the relationship between low-level arsenic exposure and bladder cancer." No significant increase in risk.
				Continuous (per 5 μg/L increase)	(odds ratio) 0.92–1.20)	
				Categorical: <1 μg/L 1-10 μg/L >10 μg/L	 1.0 (ref) 0.84 (0.63–1.12) 1.10 (0.65–1.86)	
Chen et al. 2010 (NE Taiwan)	Cohort	8,086 (12 years follow-up)	Total urinary tract cancers (n=45) Urothelial Cancer (n=36) Bladder Cancer (n=23)	As concentration in water (μg/L): <10 10-49.9 50-99.9 100-299.9 ≥300 Unknown	Urothelial Cancer: 1.00 (ref) 1.85 (0.45-7.61) 2.19 (0.43-11.1) 5.50 (1.39-21.8) 10.8 (2.90-40.3) 4.34 (1.06-17.7) p-trend<0.001	Results from analyses of cumulative exposure were imprecise (very wide confidence intervals). Statistically significant relative risk (hazard ratio) at ≥100 μg/L. No evidence of a monotonic "dose-response" pattern for younger age since started drinking or older age at stopped drinking water.

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Reference (Study Location)	Study Design	Study Size	Cancer Site (sites)	Study-Specific Exposure Categories	Relative Risk Estimate (95% CI)	Comments
Lung Cancer						
Chen et al. 2009 (NE Taiwan)	Cohort	6,888 (11 years follow-up)	Lung cancer (n=178)	As concentration in water (μg/L): <10 10-49.9 50-99.9 100-299.9 $\geq$300	 1.00 (ref) 1.10 (0.74-1.63) 0.99 (0.59-1.68) 1.54 (0.97-2.46) 2.25 (1.43-3.55) p-trend = 0.001	Analyses of cumulative exposure suggested possible threshold for arsenic exposure in relation to lung cancer. Statistically significant relative risk (hazard ratio) at $\geq$300 μg/L. No evidence of a monotonic "dose-response" pattern for younger age since started drinking or older age at stopped drinking water.
Heck et al. 2009 (New Hampshire & Vermont, US)	Case-Control	223 lung cancer cases 238 pop. controls	Lung cancer	Toenail arsenic concentration (μg/g): <0.05 0.05 to <0.0768 0.0768 to <0.1137 $\geq$ 0.1137	 1.00(ref.) 1.34 (0.71-2.53) 1.10 (0.55-2.20) 0.89 (0.46-1.75)	Analyses restricted to small cell and squamous cell cases (n=75) produced higher but less precise odds ratios (see Table 3 in Heck et al. 2009). Although toenails represent exposures from previous year (approx.), mean duration of residence was 17 years at same address
Mostaf et al. 2008 (Bangladesh)	Case-Control	3223 lung cancer cases 1588 controls (with non-malignant lung lesion)	Lung cancer	Arsenic concentration in water (μg/L): 0 to $\leq$10 11 to $\leq$ 50 51 to $\leq$ 100 101–400	ORs for male non-smokers: 1.0(ref) 0.90 (0.62-1.33) 1.10 (0.62-1.96) 0.94 (0.62-1.41)	All subjects underwent lung biopsy in 2003-2006 and case/control status was determined from results. From Results: "For the 817 women there was no clear trend between lung cancer and arsenic concentration in the drinking water of the district in which they lived."
				As concentration in water (μg/L): 0 to $\leq$10 11 to $\leq$ 50 51 to $\leq$ 100 101–400	ORs for Male smokers: 1.0(ref) 1.25 (0.96-1.62) 1.37 (0.92-2.03) 1.65 (1.25-2.18)	"The pattern in smoking women, although based on small numbers, was thus essentially that shown…for men. In women, as in men, there was no such trend in the non-smokers."

Some specific features of some of these studies are important to consider. The cohort study by Chen et al. (2010) is an update of the analysis by Chiou et al. (2001), which is summarized in the draft IRIS document (U.S. EPA 2010b). Most of the "weaknesses" identified by EPA have been addressed in the updated analysis. For example, cancer cases in the updated analysis (Chen et al. 2010 and Chen et al. 2009) were identified via the national cancer registry rather than from "various community hospitals." Furthermore, there is an additional 10 years of follow-up time since the previous publication, and mean follow-up time is now 11.6 years. As discussed previously, the weakness of "recall bias" should not apply in this cohort study. It is likely that information on two of the important potential confounding factors identified by EPA, age and gender, would not be differentially reported anyway (i.e., reporting or ascertainment of age and gender information is generally not considered 'subjective' and any errors would likely be random and non-differential with respect to disease status). The final weakness listed by EPA is that arsenic in food is not measured and this could result in misclassification, particularly in the low exposure areas. While this may be true, it is not clear how this would affect the hazard ratios or what the magnitude of bias would likely be. Before this study is dismissed as having "no potential utility," a more careful examination (e.g., sensitivity analysis) to explore the potential impact of this hypothetical bias would seem prudent.

3.2 Meta-Analyses

In addition to the studies listed above, two meta-analyses have been published: Chu and Crawford-Brown (2006, 2007), and Mink et al. (2008). Limitations of the Chu and Crawford-Brown meta-analysis have been summarized (Brown 2007b; Crawford-Brown 2007; Mink et al. 2008). **The purpose of our meta-analysis was to examine the potential association between low-level exposure to arsenic in drinking water and bladder cancer, using meta-analysis to improve precision and increase statistical power (Mink et al. 2008)**. The summary relative risk estimate in the meta-analysis restricted to data from never-smokers was less than 1.0 (SRRE = 0.81; 95% CI: 0.60–1.08; *P*-value for heterogeneity = 0.94). The SRRE for analyses of never-smokers and ever-smokers combined was slightly but not significantly elevated (SRRE = 1.11; 95% CI: 0.95–1.30, *P*-value for heterogeneity = 0.21). For analyses restricted to smokers, the SRRE was also slightly elevated, but there was evidence of heterogeneity across the studies and results should be viewed with caution (SRRE=1.24; 95% CI: 0.99–1.56, *P*-value for heterogeneity = 0.03). In the published meta-analysis (Mink et al. 2008), we evaluated whether the SRREs that resulted from the epidemiologic studies of low-level arsenic exposures and bladder cancer were in the range of 1.2–2.5 predicted by dose-response curves estimated from results from the Taiwan studies (NRC 2001). **For non-smokers the SRRE and the upper bound of the 95% confidence limit were below 1.2 (the lower bound of the range predicted in the NRC models).** In fact, the majority of the SRREs reported in our paper were below 1.2. The exceptions were the SRREs from the analyses restricted to ever smokers.

We updated our meta-analysis to include the two studies of bladder cancer listed in Table 1. Because Chen et al. did not stratify on smoking status, their study is included only in the updated analyses restricted to ever smokers and never smokers. As mentioned previously, Chen

et al. (2010) is an update to Chiou et al. (2001) and therefore Chiou et al. was removed from the updated analyses.

The overall pattern of results did not change much (Table 2). The 95% confidence interval corresponding to the SRRE for the analysis of never-smokers became narrower, indicating an improvement in precision. The SRRE for ever-smokers was somewhat attenuated, but there was still evidence of heterogeneity. In both the previous and the updated meta-analysis, the results for never-smokers are the most robust. Indeed, for the purpose of dose-response assessment, these data from never smokers should provide statistically stable estimates. These findings in combination with the consistency of the findings for never-smokers in the individual studies indicate that low level exposure to arsenic in drinking water alone is unlikely to contribute to a significant increase in bladder cancer incidence. Furthermore, our results for never-smokers were well below the relative risks predicted by NRC (2001) based on high dose exposure in Southwest Taiwan. Following the logic presented in the draft IRIS document regarding exposure misclassification and lack of power at low doses causing bias to the null and decreased statistical significance, **it is quite possible that with increased statistical power and precision, the relative risk estimates for the lowest exposure groups would indeed achieve statistical significance, and would be statistically significantly below 1.0.**

Table 2. Updated Meta-Analysis of Mink et al. (2008).

Analysis	SRRE	95% CI	P-value for Heterogeneity
Never smokers	0.83	0.65–1.06	0.894
Ever smokers	1.19	0.97–1.45	0.038
All subjects	1.12	0.95–1.32	0.026

The database from low-exposure populations is growing and many of the issues that are raised in the draft IRIS document (U.S. EPA 2010b) have been addressed in more recent, updated studies (e.g., Chen et al. 2009, 2010). Furthermore, the draft IRIS document has indicated that the data from the Taiwan studies, while imperfect, still have utility. It has not been demonstrated why data from other imperfect studies could not also be utilized.

4.0 Charge Question 2: Dose-Response Modeling

The dose-response assessment presented in the draft IRIS document uses a low-dose linear (Poisson) model in which the lower end of the curve originates at the data point for a comparison population representing all of Southwest Taiwan. **The combined effect of this approach, however, largely ignores the shape of the dose-response relationship at low doses based on this database, the consistent weight of evidence from other epidemiological studies at low doses, and mechanistic data on the mode of action of arsenic carcinogenicity indicating threshold or sublinear dose-response relationships.** Using a nonlinear approach

based on the weight of evidence is consistent with the 2005 EPA cancer risk guidelines even when uncertainty is present concerning the exact mode of action (U.S. EPA 2005). Although the 2007 SAB did not acknowledge this part of the 2005 cancer risk guidelines, they did recommend that the effect of nonlinear models be considered as well.

4.1 Effect of Comparison Population and Linear Dose-Response Modeling

The dose-response model presented in the draft IRIS document uses a low-dose linear model and anchors the lower end of the dose-response curve at the data point for the Southwest Taiwan regional comparison population, assuming this region has zero arsenic in drinking water (p. 120; U.S. EPA 2010b). Anchoring the lower end of the dose response curve at the data point for the comparison population was shown by Morales et al. (2000) to result in linear or supralinear curves rather than the sublinear to threshold shape of the actual Southwest Taiwanese data at low doses (Figure 1). Brown (2007a) likewise showed that anchoring the relationship with the comparison population essentially ignores the shape of the data in Southwest Taiwan at low doses (e.g., water concentrations <150 μg/L). The draft IRIS document presents a limited sensitivity analysis that reports that use of the comparison population does not make much of a difference (e.g., at most an 88 percent decrease in risk for female bladder cancer without the comparison population; page 139). However, this analysis uses the full range of the well water concentration data and the low-dose linear model. As can be seen in Figures 1 and 2, whether or not a comparison population is used has less of an effect if a linear relationship is forced through the data. A linear model is also is largely insensitive to the shape of the data at low doses and essentially is extrapolating from the point of departure at high doses.

SAB (2007) recommended that EPA test the sensitivity of the model to the choice of the reference population (Southwest Taiwan) and to the assumption of linearity by also using an alternative hazard model with a dose contribution that is multiplicative and nonlinear in form. However, the sensitivity analysis presented in the draft IRIS document (pp. 139–140) is limited and constrained, and consequently does not show the full effect of the various assumptions in combination. **For transparency in showing the full effect of these assumptions, the draft IRIS document should present a more comprehensive sensitivity analysis that shows the effect of using non-linear models with and without the comparison population. The draft IRIS document also lacks transparency in showing how the dose response approach selected compares visually to the actual data points.**

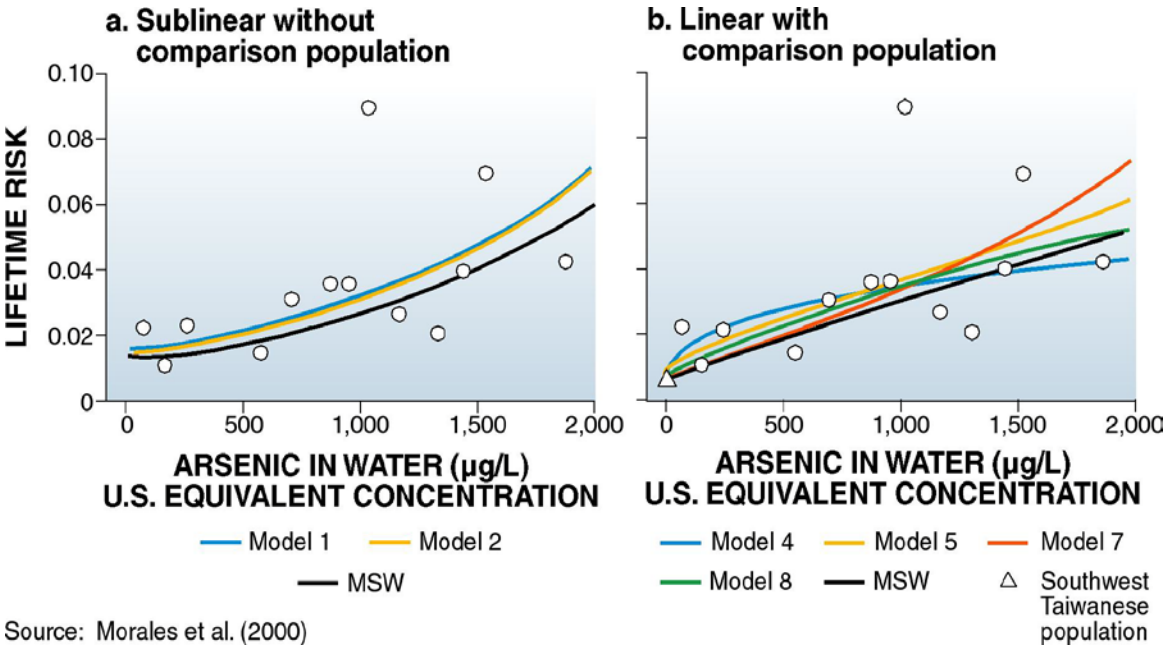

Figure 1. Effect of using a comparison population on the shape of the dose-response relationship for lifetime risk of bladder cancer mortality in males with arsenic in well water of Southwest Taiwan. Data points are for villages grouped by 50 μg/L increments, i.e., 0–50, 50–100 μg/L, etc. Modeling was conducted on the full data set (MSW=multistage-Weibull model).

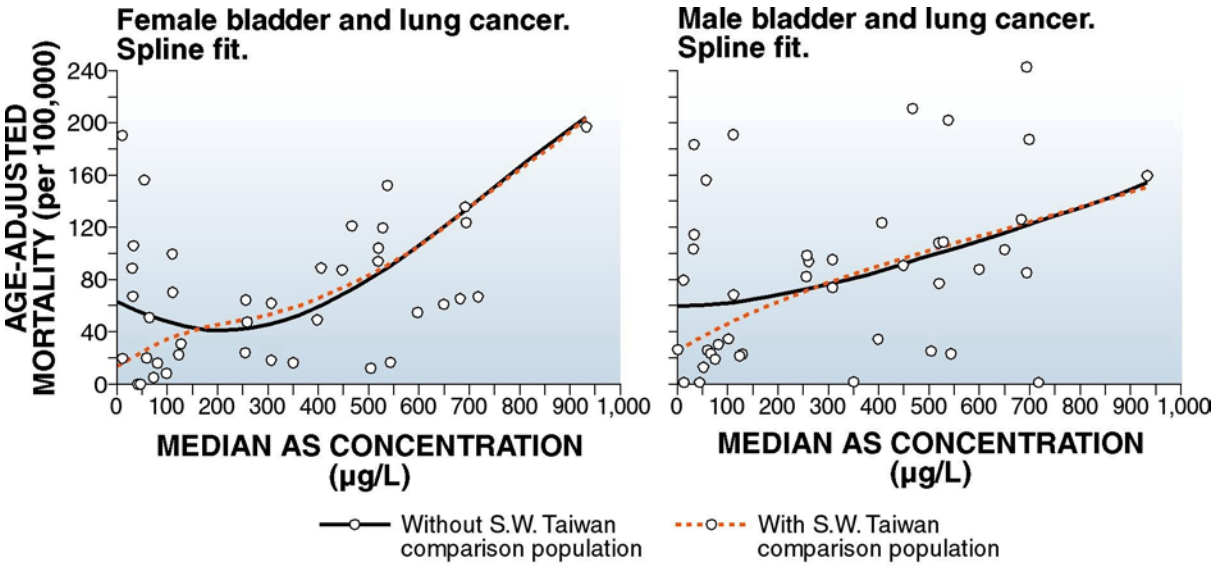

Figure 2. Comparison of the dose-response relationship for mortality of bladder and lung cancer combined with and without a comparison population for Southwest Taiwan.

The draft IRIS document also shows an analysis for the low dose region of the data (<127 μg/L; p. F-6) using the Poisson regression methodology and states that all endpoints (bladder, lung, or bladder and lung combined) for both sexes have significantly positive "b" coefficients indicating a positive dose-response relationship. This evaluation, however, is **not** shown with and without the comparison population. **Without the comparison population, these low dose relationships would likely not be statistically significant and may not even have a positive slope**.

4.2 Evidence Indicating that the Comparison Population is Inappropriate or Needs Adjustment for the Arseniasis Endemic Area

NRC (1999, 2001) and EPA in 2001 (66 Fed. Reg. 6976–7066) recognized that use of a comparison population resulted in a supralinear dose-response curve for which there is little biological basis compared to a sublinear dose-response. Also recognized was that potential differences other than arsenic exposure between the study population and comparison population could affect the results.

> *A potential disadvantage, however, of using an external comparison group* ***is that the analysis can be biased if the study population differs from the comparison population in important ways.*** (p. 190; NRC 2001; emphasis added)

> *In general, estimated ED_{01}s tend to be lower for models that included an external comparison population, primarily because the* ***lung and bladder cancer rates seen in the comparison populations were much lower than rates seen even in the study villages with low exposures****.* (p. 191, NRC 2001; emphasis added).

Although EPA in the 2001 final drinking water rule for arsenic (66 Fed. Reg. 6976–7066) decided against using the comparison population, NRC (2001) recommended using a comparison population largely based on 1) the results of Tsai et al. (1999), which showed that cancer risks were similar whether the study population was compared to a Southwest Taiwan comparison population or an all of Taiwan comparison population, 2) uncertainty in mechanistic data at that time, and 3) the possibility of exposure misclassification affecting the dose-response relationship for the study area. Nevertheless, although according to NRC (2001), the Southwest Taiwan region is more similar to the arseniasis endemic area in having a rural lifestyle compared to more urban areas of Taiwan,[1] Tsai et al. (1999) do not mention whether this whole region is as impoverished with the severely undernourished conditions of the arseniasis endemic villages. Such nutritional deficiencies have been shown to increase the toxicity of arsenic in this population and others (e.g., Chen et al. 2001; Milton et al. 2004; Mitra et al. 2004; Gamble et al. 2005, 2007; Spallholtz et al. 2004; Yang et al. 2002; Miyazaki et al. 2005). Moreover, Tsai et al. (1999) found the arsenic-exposed villages compared to these other referent populations had significantly increased cancer mortality from all causes and many other cancers (e.g., brain, bone, nasal cavity, colon, intestine, stomach) that were not consistently related to arsenic in the wealth of other epidemiological studies on arsenic at high doses. **Significantly increased risk**

[1] This area includes the counties of Chiaya and Tainan which also have urban areas. Tainan City was the first capital of Taiwan established by the Dutch in the early 1600s. The assumption of equivalence in socioeconomics between the study area townships and the comparison population region should be examined.

of cancer from all causes as well as non-arsenic related cancers is indicative of poorer health conditions or other factors than arsenic that might be increasing cancer risk for the arsenic exposed areas.

Differences in cancer risk between the study population and the Southwest Taiwan comparison population are very apparent, with the study population having much higher cancer risks at arsenic water concentrations similar to the comparison population (see Figures 1, 2). Despite the assumption by the draft IRIS document, arsenic water concentrations for the comparison region are not zero, and are likely similar to those of many of the low dose villages.

NRC (2001) and the draft IRIS document suggest that the comparison population is needed because exposure misclassification has caused a lack of dose-response relationship at low doses in the arsenic exposed villages. Exposure misclassification is a serious problem for the Southwest Taiwan study population because the median well water concentration was used to represent exposure for a village despite large variation in well water concentrations among wells within many study villages. However, as noted above, exposure misclassification does not always bias associations toward the null (i.e., toward a relative risk of 1.0) nor would it always produce a lack of a dose-response relationship particularly for continuous data such as arsenic in drinking water.

The dose-response relationship for the arsenic-exposed villages can also be examined in villages that are less likely to be affected by exposure misclassification from variation in well water concentrations. Exposure misclassification is expected to be less of a problem for villages with a single well or multiple wells with low variation in arsenic concentration than for villages with multiple wells with large variation in arsenic well water concentrations. Results for these "low variation" villages may thus be more reliable. **Bladder and lung cancer risks combined in males or females for the 23 "low variation" (variation of <25 μg/L) villages indicated no dose-response relationship and large dispersion of the cancer risk data over the range of arsenic well water concentrations** (Brown 2007a)**.** By contrast, the 19 "high variation" (variation >24 μg/L) villages, which should be more prone to exposure misclassification, indicated more of a dose-response relationship (particularly for females) with a gradual increase in risk at low exposures then a steeper increase at higher median well water concentrations (e.g., >200-300 μg/L; Brown 2007a). **Therefore, the available data do not indicate that exposure misclassification is the cause of the lack of dose-response relationship at low doses in the arsenic-exposed villages, and may instead have contributed to a positive dose-response relationship.**

The draft IRIS document conducts a sensitivity analysis by using the maximum, minimum, or median well water concentration within villages. SAB (2007) recommended other measures than the median be used, such as 10th, 20th, 80th, 90th percentiles, but **not** extremes such as maximum or minimum concentrations in a village. The exposure assessment should have also considered the difference in results between low versus high variation arsenic concentration villages as well as used measures such as average well water concentrations within villages. Unlike the median, the average is affected by the higher arsenic concentrations in a village as is the risk of cancer mortality. EPA guidance for calculating exposure concentrations (U.S. EPA 1992) notes that the arithmetic average concentration is a more appropriate estimate of an

individual's long-term exposure and that central tendency estimates (e.g., geometric mean or median) bear no logical connection to cumulative intake and may be much lower than the arithmetic average. The same is true for population exposures to arsenic related to cancer risk. Because cancer cases within villages are more likely to be associated with individuals with high arsenic exposures than lower exposures, use of a measure like the median or minimum, which is not affected by the magnitude of the higher exposure concentrations within villages, is inappropriate for exposure assessment in assessing risk of cancer.

4.3 Recommendations for Dose-Response Assessment

1. Conduct and report a full sensitivity analysis of model shape (e.g., linear, non-linear), with and without the comparison population, for the whole dose-response range as well as the lower dose region (e.g., <100 to 200 μg/L).
2. Evaluate and report the effect of using an area term in the analysis that accounts for the underlying difference in risk for the comparison population versus study area villages, which appears to be unrelated to arsenic exposure.
3. Conduct and report an exposure assessment based on average well water concentrations as well as the percentiles requested by SAB (2007) (10th, 20th, 80th, 90th percentiles).
4. Incorporate elements of a weight of evidence evaluation in the dose-response assessment including the wealth of epidemiological studies and mode of action information on arsenic carcinogenicity, as allowed by the EPA Cancer Risk Guidance (U.S. EPA 2005) and report results of the evaluation.

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