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March 29, 2010

EPA Science Advisory Board
1200 Pennsylvania Avenue, NW.,
Washington, DC 20460
Attn: Dr. Sue Shallal, Designated Federal Officer

Subject: SAB Workgroup of the Chartered Science Advisory Board: EPA draft "Toxicological Review of Inorganic Arsenic" [FR 75(39) 92015-06]

Submitted electronically

The Electric Power Research Institute appreciates this opportunity to provide written comment on the February 2010 draft of the Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS) [EPA/635/R-10/001] and to raise questions that may assist the Science Advisory Board (SAB) Workgroup in its expedited review of the current draft.

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Attachments

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Comments by the
Electric Power Research Institute
on the February 2010 Draft
Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)
In Response to the Proposed Charge to the SAB Workgroup

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Introduction

The Electric Power Research Institute (EPRI) appreciates this opportunity to comment on the February 2010 draft of the *Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS) [EPA/635/R-10/001]* and (hereafter referred to as the "*Toxicological Review*") to raise questions that may assist the Science Advisory Board (SAB) Workgroup in its expedited review of the current draft (USEPA 2010). EPRI has been involved for many years in research to ensure that the toxicity of arsenic compounds is thoroughly characterized. This work has included the sponsorship of a number of studies published in peer-review journals reporting on the continuing investigations of the potential mode(s) of action (MOA) for the toxic effects of arsenic compounds (Wiencke & Yager, 1992; Yager & Wiencke, 1993; Mann et al., 1996a; Mann et al., 1996b; Crecelius & Yager, 1997; Yager & Ostrosky-Wegman, 1997; Gonsebatt et al., 1997; Del Razo et al., 1997; Tice et al., 1997; Wiencke et al., 1997; Yager & Wiencke, 1997; Broeckaert et al., 1997; Yager

et al., 1997; Broeckaert et al., 1999; Gentry et al., 2004; Gentry et al., 2005; Kedderis et al., 2006; Clewell et al., 2007; Kenyon et al., 2008; Gentry et al., 2010). In addition, EPRI has worked cooperatively with the USEPA to fund critical research related to the pharmacokinetics and genomics of arsenic compounds including work via a memorandum of understanding initiated in 2005 (see EPRI Comments Appendix A). On-going EPRI-supported research continues on investigating the human cellular responses that parallel responses in animal models based on an *in vivo-in vitro*, or parallelogram, study design focused on the bladder as the target organ. Toxicological pathways of MOA continue to be examined at the gene level in order to address dose-response-time dimensions using functional gene expression microarray technology (Gentry et al. 2010; Clewell et al. 2008; Yager et al. 2010). Results will then be applied in combination with previously developed mouse and human pharmacokinetic data to build a novel biologically based human health cancer risk evaluation for exposure to low levels of arsenic. The anticipated date of completion of this work is late 2010 to early 2011.

EPRI understands that the development of the current draft *Toxicological Review* has been a long process, approximately six years since completion of the first draft document (as outlined at USEPA 2009), and three years since release of comments from the last external peer review originally initiated in 2005 (SAB 2007). During this period, an extensive number of studies have been published; and, although the current draft *Toxicological Review* summarizes the majority of these studies, the available quantitative assessment is nonetheless based on data generated almost two decades ago from a Taiwanese population with well-documented limitations (Chen et al. 1988, 1992; Wu et al. 1989).

Our comments are focused on the scientific issues related to the three charge questions addressed to the 2010 SAB Arsenic Workgroup. EPRI provides these comments on issues that we respectfully request the SAB Workgroup examine as part of their review of the *Toxicological Review*. As will be discussed in detail under each charge question below, the scientifically justified alternative assumptions and modeling approaches to those used in the current draft of the *Toxicological Review* (USEPA 2010) will have a significant impact on the estimation of the potential risk to human health following exposure to low concentrations of arsenic compounds. These comments focus on several main points for consideration by the SAB Workgroup including:

- A critical review of all arsenic epidemiological drinking water studies has not been conducted that uniformly apply specific criteria to each individual study (as recommended by the SAB in 2007).
- Additional consideration of several important epidemiological studies currently removed from consideration for quantitative assessment, and thereby limiting the information available to characterize the low-dose region of the dose-response curve.
- Further review of several more recent epidemiological studies, including additional studies from the Taiwanese populations (Chen et al. 2009; 2010), that can provide additional information to characterize the shape of the dose-response curve in the low-dose region.
- Recognition that additional information is still needed to support many of the assumptions and approaches incorporated in the dose-response assessment of the *Toxicological Review* including the epidemiological study selection; the evaluation of exposure-response from the Taiwanese studies; the methodology applied to combining cancer unit risk estimates; the incorporation of the impact of smoking, the relative ability

to integrate the available data from low-dose studies for dose-response analyses; the selection criteria for the arsenic exposure dose metric applied; and, the handling of the SAB conclusions related to DMA carcinogenicity and arsenic MOA.

- Although a sensitivity analysis was conducted, it lacks adequate discussion on the potential impact of the assumptions applied, such as the referent population and non-water intake of arsenic, capable of influencing the cancer unit risk estimate.

It is our intent to: 1) provide these data and raise these questions as the SAB Workgroup evaluates the wealth of data on these complex issues; and, 2) assist the SAB Workgroup in the integration of these data. As such, the final *Toxicological Review* will reflect the state-of-the-science, and be recognized by all stakeholders as scientifically defensible.

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

1. Application of Uniform Criteria in the Critical Review of the Epidemiological Literature

The SAB (2007) Arsenic Review Panel specifically recommended that a critical review be conducted of all arsenic drinking water studies by uniformly applying specific criteria to each individual study. The recommended uniform criteria were the following (SAB 2007, p. 39):

- estimates of the level of exposure misclassification;
- temporal variability in assigning past arsenic levels from recent measurements;
- the extent of reliance on imputed exposure levels;
- the number of persons exposed at various estimated levels of waterborne arsenic;
- study response/participation rates;
- estimates of exposure variability;
- control selection methods in case-control studies; and,
- influence of these factors on the magnitude and statistical stability of risk estimates.

The SAB (2007) further recommended that results of the uniform critical criteria analysis be presented in a table format in order for the results and rationale for accepting or excluding specific epidemiology studies to be transparent. Although the *Toxicological Review* draft document summarizes epidemiology studies in a table format (in Appendix B of USEPA 2010), a systematic evaluation using the specific criteria recommended by the SAB (2007) has not been applied or documented to each study as recommended.

For example, in the *Toxicological Review*, Tables B-1 through B-8, the availability of smoking status is occasionally stated as a strength for studies that include smoking-adjusted analyses (Guo et al., 1997, 2004; Chiou et al., 2001); and, as a study weakness if data were not collected (Morales et al., 2000). However, the availability of smoking status remains unavailable in the critical review of each study, including in many of the Taiwan-based studies utilized to derive the cancer slope factor (CSF) (see USEPA 2010 Appendix Table B-1, but includes Chen et al., 1988, 1992; Wu et al. 1989). This is a significant omission (see later section for further

discussion), since a large body of epidemiological literature has documented smoking behavior as a co-carcinogenic or synergistic factor in bladder and lung cancer causation. Furthermore, not accounting for the impact of population migration on study outcome is cited as a weakness for one study (Marshall et al. 2007), however, impact of migration (15% population decrease from 1973-1986) is also unaccounted for in southwestern Taiwan studies (again includes Chen et al., 1988, 1992; Wu et al. 1989 among others). There are numerous additional examples of inconsistent application of evaluation criteria in Tables B-1 through B-8 resulting in lack of coherence in ranking studies for their value in estimating risk particularly estimates of the relative level of exposure misclassification and discussion of its potential influence on the reported risk estimates.

Table 1 (see below) provides an example to demonstrate how results from a few recently conducted prospective cohort studies on lung and bladder cancer outcomes associated with arsenic drinking water levels can be uniformly evaluated on the specific recommended criteria (SAB, 2007). For comparison, an evaluation is also presented for two of the ecological studies from southwest Taiwan using the same criteria relied on by the USEPA (Chen et al., 1992; Wu et al., 1989).

Construction of a similar table encompassing all epidemiology studies is recommended, specifically structured around studies grouped by study design. Such a table should begin with ecological studies as the weakest design, followed by case-control studies, and finally prospective cohort studies as the strongest study design. As seen from Table 1, inter-study strengths and weaknesses can be more easily discerned and via individual study characteristics described by a uniform set of criteria ranked in terms of usefulness for estimating cancer.

From this abbreviated table characterizing only a limited number of studies, it appears that more recent prospective studies focusing on individual exposure measures at lower levels of arsenic in drinking water have a major design advantage over ecological studies. Specifically, this advantage lies in classifying individuals in the cohort in relation to arsenic levels in drinking water before disease develops. As such, prospective studies provide considerably less bias in determining exposure, and yield incidence rates as well as relative risk estimates. Recent studies with lower arsenic levels have yielded relatively consistent results across different investigators and different study populations (Baastrup et al., 2008; Chen et al., 2009, 2010; Michaud et al., 2004).

In many of the study summaries provided within the *Toxicological Review*, the limitations cited by the study authors in the published discussion section are recounted in the USEPA draft, but without any attempt to critically evaluate the basis of these limitations and their impact on interpretation of study results. To conduct an unbiased, critical evaluation would require a standard set of criteria for judging the quality of a study, as recommended by the SAB (2007). As noted above, no such set of criteria was developed or applied in the current draft. The USEPA in response to the SAB's request for a uniform set of criteria should not only have developed such a list, but should also have developed a scheme to weight these criteria in order to provide a consistent, comparative, critical review of the merits and shortcomings of each study; and to document relative findings in the supporting review in a readily apparent manner.

Typically, discussion sections of studies in the published literature outline limitations or caveats attached to the research. The authors also typically discuss the impacts of limitations on the outcome and conclusions of the study. The *Toxicological Review* does not provide a discussion of whether such "weaknesses" would invalidate the use of specific data qualitatively or quantitatively. Thus, in addition to the lack of a "uniform set of criteria", there is no critical evaluation of the impact of any of these limitations on the validity of the study conclusions or the usefulness of these data in a quantitative cancer assessment. The SAB (2007) specifically requested that the USEPA should consider "the influence of these factors on the magnitude and statistical stability of risk estimates." Not all of these limitations are likely to have equal impact on conclusions related to the carcinogenic potential of inorganic arsenic in the United States (U.S.). For example, not controlling for subjects' smoking in the Taiwanese studies likely results in a greater impact on the outcome (bladder cancer) than not controlling for smoking in the Utah population reported by Lewis et al. (1999) due to substantial differences in the population prevalence of such a strong cancer risk factor (smoking) between the two study areas.

It is important to note that many of the "weaknesses" of the epidemiological studies described in the *Toxicological Review* appear applicable to the Taiwanese data used to derive the arsenic cancer unit risk (UR), as well as being inherent in the conduct of any epidemiology study (e.g., some degree of exposure misclassification). Unfortunately, once more not all of the "weaknesses" of a study were consistently identified or defined in the text or in the table in Appendix B of the *Toxicological Review* across all studies. For example, an identified weakness in the Lamm et al. (2004) study or the Morales et al. (2000) reanalysis of the Taiwanese populations was the lack of available individual arsenic exposure data. However, individual exposure data were also not available for a number of other studies including work by Guo et al. (2001, 2003), which was another reanalysis of some of the Taiwanese data set, and in the specific studies relied upon in the *Toxicological Review* for the quantification of the potential for cancer, i.e., Chen et al. (1988, 1992) and Wu et al. (1989). Controlling for smoking (discussed in later sections), a known cause of both lung and bladder cancers, or measurement of non-water sources of arsenic exposure, was only conducted in a limited number of studies. However, in the *Toxicological Review*, neither study characteristic was consistently mentioned as a study weakness, including most prominently for the Taiwanese studies relied upon to develop the CSF for inorganic arsenic.

Consideration of non-water sources of arsenic, in particular dietary sources, was listed as a weakness in selected epidemiological studies (Chiou et al., 2001; Morales et al., 2000) even though this factor is a common element in most of the studies evaluated (including Chen et al. 1988; Wu et al., 1989). Lack of measurement or adjustment for a non-water source appears to be a reason to exclude non-Taiwanese studies from further quantitative consideration; however, the Taiwanese data used in the derivation of the CSF contain the same characteristic weakness.

Another limitation broadly applied to all non-Taiwanese studies, and particularly to those in which drinking water exposure levels were <50 ppb, was the potential for "misclassification bias", which the *Toxicological Review* suggests directionally biases results toward the null hypothesis of no effect. However, in studies with a large sample size, such as Baastrup et al. 2008, misclassification bias will have minimal impact on study outcome (NRC 2001). Therefore, the finding of no increased cancer risk at multiple sites including lung and bladder in a cohort

study of 56,378 Danish individuals whose arsenic exposure ranged from 0.05 ppb to 25.3 ppb (Baastrup et al., 2008) as the result of possible exposure misclassification bias does not serve as a substantive basis for dismissal of this study from further consideration in characterizing the dose-response curve at the low environmental exposure levels particularly relevant to U.S. populations.

2. Selection of the Critical Epidemiological study for Use in the Dose-Response Assessment

The *Toxicological Review* states that "In keeping with SAB's recommendations, epidemiological studies by Smith et al. (1998) and Ferreccio et al. (2000) on arsenic-related lung cancer in Chile, as well as studies by Chiou et al. (2001) and Chen et al. (2004), were evaluated (see Section 4.1 and Appendix B of USEPA 2010); however, these studies were not considered to be of comparable quality to the Taiwanese data set for use in developing the CSF". However as mentioned previously, the specific criteria of the USEPA to make this quality determination are not readily apparent in the document. Consideration of additional studies was recommended by the SAB (2007); however, because the USEPA did not define "not considered acceptable" for the Chiou et al. (2001) and the Ferreccio et al. (2000) papers, or for any of the other studies not considered in the quantitative analyses, this lack of transparency leads to speculation as to the fundamental basis for exclusion. Without supporting documentation, simply stating that the published data were not adequate to perform quantitative analyses does not provide a comprehensible, logical and transparent basis for such exclusion decisions.

In reviewing the draft inorganic arsenic *Toxicological Review*, it appears that access to unpublished data not present in the published versions of Chen et al. (1988, 1992) or Wu et al. (1989) was available in order for the Chen et al. (1992) to now be considered acceptable and to conduct the analyses discussed in the dose-response section. Use of individual "raw" data, which is typically not available in publications, is usually the preferred approach when developing toxicity values using epidemiological data and in some cases when using animal data, such as time-to-tumor information. The issue, however, remains transparency.

Even if the published data for arsenic exposure in other populations may not be as detailed or in the appropriate format, in previous assessments USEPA has worked with the study authors of the critical studies to obtain these individual data (while protecting privacy concerns). None of the discussion in the *Toxicological Review* indicates an attempt to explore gathering additional individual data for other studies, despite the fact that several studies with populations exposed at identifiably lower arsenic levels could have been used to define the shape of the dose-response curve in the low-dose region (including but not limited to Baastrup et al., 2008; Ferreccio et al., 2000).

A number of epidemiological studies in both the U.S. population and other countries, including Taiwan, have clearly demonstrated that cancers at the designated target tissues, bladder, lung, and liver – did not increase with chronic exposure to low concentrations (<100 ppb) of inorganic arsenic in drinking water (Chiou et al., 2001; Guo 2003; Ferreccio et al. 2000; Baastrup et al. 2008; Bates et al. 1995; Steinmaus et al. 2003; Lamm et al. 2004; Karagas et al., 2004; Meliker et al. 2007; Lamm et al. 2007; Mostafa et al., 2008; Heck et al., 2009; Chen et al., 2009; Han et al., 2009). The dismissal of these studies from further quantitative consideration based on their

presumed "weaknesses" appears inconsistent with rigorous scientific reasoning, as discussed previously. Specifically, all of the epidemiological studies, in particular those from the endemic regions of Taiwan that have been used over the years to quantify the risk of cancer from ingestion of inorganic arsenic via drinking water, have the same general weaknesses. However, several non-positive studies have design strengths absent from the high dose Taiwanese data including the following:

- Population demographics more characteristic of the U.S. population;
- Consideration of smoking as a confounding variable (either directly or indirectly by evaluation of a U.S. population with low smoking prevalence);
- Better characterization of arsenic exposure (i.e., data from individual wells or municipal water supplies used by the subjects versus retrospective geographic assignment based on village-level well arsenic concentrations); and,
- Use of cancer incidence versus mortality data to quantify outcomes.

Two of the studies with data in the low-dose range, Chiou et al. (2001) (bladder cancer) and Ferreccio et al. (2000) were considered to be of lower quality in the *Toxicological Review*. However, the NRC (2001) concluded that these two studies were of sufficient size and quality; and contained adequate quantification of exposure to be considered in computing effective dose (ED) for arsenic in drinking water. As with other studies of low-dose arsenic exposure, the *Toxicological Review* provides no justification for exclusion; and, no indication of any attempt to use these studies to quantitatively extend the shape of the dose-response curve into the low-dose region via an integrated approach.

In addition, the SAB (2007) concluded that the body of data for inorganic arsenic "strongly suggests the possibility of a threshold for arsenic carcinogenicity" (SAB 2007, p. 6). The SAB further concluded that there is substantial evidence to illustrate that exposure-response to arsenic appears non-linear at low environmental concentrations (i.e., < 100 ppb in drinking water) as cited in its report (Baastrup et al. 2008; Lamm et al. 2004). Studies such as Baastrup et al., (2008) should at least be used to calculate an upper limit on the CSF in the low-dose region, and to better characterize the overall shape of the dose-response curve. The current risk estimates provided in the *Toxicological Review* for arsenic-associated lung and bladder cancer using the Taiwanese dataset is inconsistent with conclusions from studies conducted in the U.S. For example,

- Bates et al. (1995) in a case-control study conducted in the U.S. found no association between bladder cancer and measured arsenic exposures in the range of 0.5 to 160 ppb (mean 5.0 ppb).
- A retrospective mortality study on a Utah cohort with measured arsenic water exposures of 14 to 166 ppb found no statistically significant increases in cancer mortality (Lewis et al., 1999).
- Steinmaus et al. (2003) in a case-control study of bladder cancer in seven counties in the Western U.S. reported an odds ration (OR) of 0.94 for exposures greater than 80 µg/day, which is below the risk one would predict based on higher arsenic concentrations in the Taiwan drinking water studies.

- Lamm et al. (2004) conducted an ecological study of bladder cancer in 2.5 million persons throughout the U.S. that encompassed 75 million person-years of exposure. No significant association was noted between cancer outcomes and estimated arsenic drinking water exposure.

In isolation, the results from the studies from non-Taiwanese populations do not provide an indication of where a lower linearity threshold might be, nor do they show the shape of the dose-response curve at levels below such a threshold. In addition, a threshold has not been confirmed by epidemiological studies. However, consideration of these studies *in toto* may better define the low-dose region of the dose-response curve for inorganic arsenic and in turn provide more scientifically justifiable estimates of risk for the U.S. population.

3. Exclusion of Epidemiological Studies from Consideration Due to Statistical Power

In the *Toxicological Review*, one of the weaknesses listed for several of the epidemiological studies (e.g., Bates et al. 1995; Lewis et al. 1999; Hinwood et al. 1999) was low statistical power. The implication of this characterization is that it is difficult for most epidemiologic studies to discern the NRC-estimated cancer risks at low exposures (Ramasamy et al. 2010). Because of the low levels of risk that are the focus of EPA cancer dose-response modeling (i.e., levels on the order of one in 1 million), this is an unsupportable basis for excluding a number of studies. An additional weakness that was attributed to a large cohort study reported in Denmark (Baastrup et al. 2008) was the low concentrations of arsenic in the drinking water to which the study cohort was exposed. Low levels of arsenic exposure will never be associated with levels of risk that can be easily be "detected", that is why dose-response analysis is conducted and why model-based extrapolations are used in risk assessment.

"Detection" of the risk – that is, finding frank outcomes of morbidity and/or mortality – is not the concern in dose-response modeling. Risk estimation is the most important aspect of a risk assessment, and confidence limits on estimates of low-dose risk are the means by which one evaluates the uncertainties. Whether or not an observed response rate is "significantly" different from what one might observe in an unexposed population, that rate can (and should, provided other aspects of the study are satisfactory) be used for estimation of the risk at a range of dose levels.

Statistical power is a tool used during study design to evaluate the probability of obtaining a "positive" result (rejection of a null hypothesis), given the sample size, the test to be employed, and other factors. It is as much an evaluation of the test and it limitations as it is of the data. There is no justification for considering the power of a study after it is completed – the results of that study are what they are and whether or not the test of the null hypothesis results in the rejection of that hypothesis is a matter of fact, not of probability. However, as mentioned above, rejection or acceptance of the null has no bearing on the *estimates* that can be derived from the resulting observations. Hoenig and Heisey (2001) strongly argue against the use of retrospective power analyses and show how confidence limit calculations are a better approach. In addition, Smith and Bates (1992) demonstrate that after the completion of an epidemiological study, statistical power to detect a relative risk of interest may be recalculated resulting in the dismissal of a negative study on the grounds that its power is too low. However, these types of *post hoc*

power calculations ignore actual relative estimates and variance, which are known at the conclusions of a study. These authors demonstrate that post-study power calculations have little value and should be replaced by more informative methods using the upper confidence limit of the point estimate that overlaps the values of the relative risk of interest.

The calculations and data used to determine statistical power for these selected studies is not provided in the draft *Toxicological Review*, making it difficult for the reviewer to understand these conclusions. The equivalence of the excess and relative risks presented can not be evaluated until and unless the assumed background rates for the cancers in question are known. Power also cannot be evaluated without reference to a particular statistical test which is unidentified in the draft review. The basic unit of measurement in an epidemiological cohort study is the person-year; it is not clear if the "sample sizes" presented are for individuals or for person-years. Several attempts to replicate the sample size calculations for the various combinations of power and excess risk, using different statistical tests, failed to yield the reported results.

Because the calculations used to draw these conclusions are not clear, any conclusion that the Taiwanese studies have more statistical stability or power to "detect" risks for low arsenic levels is not evident. The conclusion has not been demonstrated to be the case, nor is it likely to be the case; as stated above, no epidemiological study is likely to be able to reject a null hypothesis for the low doses for which risk estimates are desired (e.g., 1 µg As/L). Again, that is why, even with the Taiwanese studies, modeling and dose-response extrapolations have been required, because *post-hoc* power calculations are not the appropriate basis for evaluating a completed study.

4. Identification of Hazard Associated with Low Drinking Water Concentrations of Arsenic

The SAB (2007) Arsenic Review Panel suggested that published epidemiology studies of U.S. 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. They further suggested that these comparative analyses could lead to insights into the possible influence of differences on population responses to [different levels of] arsenic in drinking water (SAB 2007, p. 7).

Regarding the Taiwanese dataset, it is important to note that there was no indication that exposures below 50 ppb had any impact on cancer risk. For example, Guo et al. (1997) determined six categories of arsenic exposure and showed no effect at exposures < 330 ppb arsenic in drinking water for any of four adverse cancer outcomes in 2,915 cases. Likewise, no effect was shown on any type of skin cancer at exposures < 170 ppb (Guo, et al. 2001). A cohort study of 2,503 residents of southeast Taiwan versus 8,088 residents of northeast Taiwan showed no increased lung cancer risk at exposures ≤ 100 ppb arsenic in drinking water (Chen et al., 2004). This information is critical to the quantitative assessment of the potential carcinogenicity of inorganic arsenic, because it demonstrates a lack of linearity in the dose-response curve.

Section 4.6.1 of the *Toxicological Review* lists the advantages of the southwest Taiwan database for use in cancer characterization and assessment, and comparison of estimated risk for other high exposure studies (Table 5-5). Yet there is still no systematic evaluation of the numerous additional epidemiology studies on the exact same criteria – and particularly those epidemiology studies in which drinking water arsenic levels are ≤ 300 µg/L. The document continues to focus on studies in which drinking levels are high (≥ 300 µg/L) while excluding information from studies in which documented drinking water values are ≤ 300 µg/L. Therefore it is recommended that future analyses conduct a rigorous weight-of-evidence critical review using identical performance criteria for each published epidemiology study and clearly describe the coherence of results (or lack thereof) between the studies. What remains lacking in the document is a clear, transparent description of the exact step-by-step rationale supporting assumptions and decisions that were made in the process of selecting data to carry out cancer risk estimates applicable to the U.S. population.

In the five years that have passed since the SAB (2007) actually reviewed the epidemiology literature on lung and bladder cancer outcomes associated with arsenic in drinking water, a number of additional studies have been published (including Baastrup et al., 2008; Chen et al., 2009; Chen et al., 2010; Marshall et al., 2007; Lamm et al., 2007). As reviewed below, and above in Comment 1, more recent studies that have documented drinking water arsenic levels ≤ 100 µg/L generally show modest or no significant increase in lung or bladder cancer associated with those levels. In general, these studies demonstrate a lack of association between lower exposure levels of inorganic arsenic in drinking water (e.g., < 100 µg/L) and bladder or lung cancer.

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

1. Continued Reliance on the Taiwanese Data for Dose-Response Modeling

In the current draft of the *Toxicological Review*, and based on recommendations made by the SAB (2007), the Taiwanese data is selected to be used for quantitatively characterizing the carcinogenic potential for inorganic arsenic based. However, it is important to note that the 2005 SAB Arsenic Review Panel offered this opinion on the usefulness of the Taiwanese data without conducting their own critical review of the available epidemiological studies. As noted on page 38 on the SAB report, the SAB states that, "To be clear, the panel did not do an exhaustive review of all possible toxicologic and epidemiologic literature during its review". In the list of epidemiology studies with exposure levels relevant to the U.S. population, SAB did not mention the study by Lamm et al. (2004) that evaluated bladder cancer in 2.5 million persons throughout the U.S. and included 75,000,000 person-years of exposure. Further, in the last five years, there are several additional studies (Lamm et al. 2007; Baastrup et al., 2008; Chen et al., 2009; Heck et al., 2009; Marshall et al., 2007; Mostafa et al., 2008; Han et al. 2008; Meliker et al. 2007; Smith et al. 2006; Kwong et al. 2009) and two meta-analyses (Chu and Crawford-Brown 2006; Mink et al., 2008) that were not considered in the 2005 draft of the *Toxicological Review* considered by the SAB (2007), and therefore not reviewed by the SAB Expert Review Panel in 2005, including

the large cohort study conducted in Denmark (Baastrup et al. 2008) which is particularly relevant for U.S. populations exposed to lower levels of arsenic in drinking water.

In addition, the SAB (2007) agreed that "at this time" the Taiwanese data set remained the "most appropriate" choice to estimate human *bladder* cancer risk, as noted in the SAB's Executive Summary. The SAB, however, qualified this conclusion with a number of recommendations including:

> (1) USEPA should conduct adjunct analyses to test the robustness of results against their assumptions;
> (2) USEPA should determine the impact of variability in some parameters compared with results from other datasets; and
> (3) USEPA should provide a transparent assessment of the available epidemiological data using a consistent set of criteria.

In reviewing the limitations described in the February 2010 *Toxicological Review* for the epidemiological data, limitations in the Taiwanese data have not been clearly and transparently described either qualitatively or quantitatively as requested by the SAB (2007) in a manner that would "help inform risk managers about the strength of the conclusions". In addition, an integrated discussion of the various re-iterations or re-analyses of the Taiwanese data is not provided which would give the reader a clear and transparent understanding of what additional information each study contributed to the overall assessment of this population.

2. Characterization of Drinking Water Exposure in the Taiwanese Study

While the Taiwanese dataset represents a long-studied population, the evaluation of the dose-response for cancers in the Taiwanese drinking water exposures is complicated by limitations in the exposure assessments performed in those studies (Brown et al. 1997). Specifically, the use of the median well concentration measured in each village can inadvertently lead to misspecification of exposures due to the extremely wide range of concentrations in the wells in many of the villages, as noted in the *Toxicological Review*.

Because of the high salinity of shallow wells in this area, the studied population used deep artesian wells for drinking water; alternative water sources did not become generally available until 1970. The arsenic concentrations in the artesian wells were much greater than those in the shallow wells. Morales et al. (2000) used the median well concentration for each village, but mentioned that individual exposures could vary widely in a village. Brown and Chen (1995) reviewed the data on well concentrations used as the basis for the exposure assessment for each village, and found that the range of concentrations was often several orders of magnitude, with lowest well concentrations around 10 to 50 µg/L and highest well concentrations around 600 to 1750 µg/L. Given this variability, the median well concentration in each village could bear a different relationship to the range of exposures across villages. For example, in one village, where the range of well concentrations was 10 to 770 µg/L, the median well concentration was 30 µg/L, while in another village, with a range from 50 to 1750 µg/L the median was 520 µg/L. Complicating the exposure estimates, many villages were under-sampled, that is, only a few wells in each village were actually tested; and, it is unclear whether this was a randomized

sampling of wells. In most villages, only five or fewer wells were tested, and in 20 villages, only one well was tested.

An evaluation of the dose-response for tumors in the Taiwanese population using this information (Brown and Chen, 1995) concluded that there was no evidence of excess risk of cancer mortality for exposure to drinking water arsenic at concentrations below 100 µg/L. An alternative study of bladder and kidney cancer incidence in the Taiwanese population, in which a more detailed exposure assessment was performed, also found evidence of a highly nonlinear dose-response (Guo et al., 1994), suggesting that a "threshold" for the carcinogenicity of arsenic may exist in the vicinity of the current Maximum Contaminant Level (MCL) for arsenic of 10 µg/L (Abernathy et al. 1996).

These studies suggest, then, that it is actually possible that all of the arsenic-induced tumors observed in the Taiwan population were in individuals exposed to concentrations well above the current MCL. One way to evaluate the implications of this hypothesis would be to assume that each of the cancer outcomes was associated with the highest well concentration in the village, rather than the median. This would provide a “lower-bound” risk estimate that could be used to bound the uncertainty associated with misclassification of exposure.

These types of questions suggest a lack of transparency in the documentation of the quantitative analyses conducted and limit the determination of any impact these assumptions may have on the outcome of the dose-response modeling for inorganic arsenic. It also limits the comparison of the current analyses to those previously conducted (NRC 2001; USEPA 2005) to determine differences in the results and if the USEPA has truly considered all of the recommendations made by previous external reviewers.

3. Current Approaches Used in the Derivation of the Recommended Unit Risk

USEPA has chosen a linear model for the arsenic dose component of the hazard representation for lung and bladder cancer, citing a lack of knowledge of the dose at which a threshold for effects may occur. In addition, various model forms were applied, as part of the sensitivity analysis, to evaluate the shape of the dose-response curve in the low-dose region. While consistency in results is discussed, what is not discussed is that this consistency may be related to the inability of the Taiwanese results to characterize the low-dose region. It should be an important issue for consideration when different model forms were not able to substantially differentiate between predictions from linear, quadratic, and exponential model forms that potentially have quite large differences in low-exposure curve shapes (see discussion on pages 114-115 of the *Toxicological Review* document). This calls into question the ability of the available data from this cohort to adequately characterize the region of the dose-response curve most critical to U.S. populations ($\leq$ 100 ppb).

In analyzing the Taiwanese data, arsenic specific dose *rate*, mg/kg/day, was used as the explanatory variable. In the majority of USEPA epidemiologically based cancer assessments (e.g., chromium), a cumulative exposure metric has been used. The rationale would be that it is the exposure duration as well as the exposure level that determines the risk; the two together define a cumulative exposure metric. Such a metric should be explored to see if the explanatory

power is better with such a metric than with the dose rate metric. An additional advantage of considering a cumulative exposure metric is that lag or latency between exposure and cancer response can be considered; this may be important for cancers like bladder cancer that appear to have a long lag between occurrence and detection.

4. Method of Combining Results for Multiple Tumor Types

The recommended Unit Risk (UR) is based on a combination of tumors (bladder and lung) as the basis for their assessment. There are several issues associated with that choice that should be addressed to correct the assessment. The calculation of an overall UR for bladder and lung tumors combined is based on a method of summing URs from multiple separate tumor types that has not been demonstrated to be appropriate. In the application of this method (Equation 5-5, p. 131 of the *Toxicological Review*), it is assumed that the estimates of the URs are normally distributed around the Maximum Likelihood Estimate (MLE) with, for example, the 95% UCL for the UR being equal to the MLE (mean) plus 1.645 times the standard error. This is incorrect for several reasons:

- In the estimation (model-fitting) procedure, it is the ED_{10} that is estimated; LED_{10} is the 95% lower confidence limit for the ED_{10}. That does not imply that the UR (defined as $0.1/ LED_{10}$) is the 95% UCL for the ratio $0.1/ ED_{10}$.
- As seen by the definition of the UR, it is a ratio of a fixed value divided by an estimate of a parameter (the concentration associated with 10% incremental risk). There is no reason to assume that such a ratio would be normally distributed around a mean value even if Benchmark Dose (BMD) estimates were normally distributed around a mean (MLE). Considering that the ratio is constrained to be positive since the BMD and BMDL by definition must be positive, it is clear that the assumption of normality is inappropriate.
- The estimation of these values using software for Poisson regression, does *not* make such simplistic assumptions (e.g., that the BMD estimates are normally distributed about an MLE). The more appropriate method is a profile likelihood procedure that identifies the likelihood of various BMD values and selects the smallest value that gives a likelihood that could not be rejected with 95% confidence.
- To state that this is a statistically based approach is therefore erroneous since the underlying assumption of the analysis (i.e. normality of the UR estimates) has not been shown to be true and, based on the type of data, that assumption is inappropriate.

5. Potential Impact of Smoking

Amid all of the discussions of arsenic's potential to cause "multiple tumors at multiple sites", the final recommendations in the *Toxicological Review* are based on the observation of cancer of the bladder and lung, two tissues known to be targets of other chemicals, especially those in tobacco smoke. In some studies that controlled for smoking, the incidence of both bladder and lung cancer was increased compared to those persons who did not smoke, presumably persons with the same arsenic concentrations in their drinking water (including Bates et al., 1995; Chen et al., 2004; Chen et al., 2009; Ferreccio et al., 2000; Kurttio et al., 1999; Michaud et al., 2004; Mostafa et la., 2008). However, because those specific data are not available, it remains difficult to separate the contribution of smoking versus the contribution from arsenic in drinking water. A

careful detailed analysis of this interaction in studies that considered smoking as a covariant was not conducted in the current draft *Toxicological Review*, i.e., at what concentration in water is this interaction between smoking and non-smoking likely to occur. There was also no adjustment in the UR for smoking for lung and bladder cancer risk, this factor having been deemed an "unquantifiable uncertainty." In relying upon the Taiwanese data, additional issues should be considered:

- Studies by Chen et al. (1988, 1992) and Wu et al (1989) did not control for smoking history – a major known risk factor for both lung and bladder cancer.
- Cigarette smokers have a decreased secondary metabolizing capacity [i.e., higher monomethylated arsenic (MMA) in urine] that may be associated with greater toxicity (Huang et al. 2007).
- Several identified studies controlled for smoking history and noted the synergistic effects of ingested arsenic and cigarette smoking on lung cancer (Chen et al. 2004; Tsuda et al. 1995; Ferreccio et al. 2000). However, these studies were not used for the derivation of the CSF.
- The *Toxicological Review* cites Smith et al. (1998) in which the investigators dismiss smoking history as a confounding factor for the mortality rate from bladder cancer in the Taiwanese population because the relative risk (RR) of bladder cancer in smokers not exposed to arsenic (RR range of 2 to 4) is less than the standardized mortality ratio for bladder cancer in an arsenic-exposed population in Chile. However, the reported smoking survey data in this study came from an unrelated cross-sectional Chilean National Survey in which participants were asked if they had smoked cigarettes over a one-month period in 1990.
- The impact of smoking on lung and bladder cancer outcomes must be addressed in this cancer assessment based on numerous prior studies on this variable and its known impact on these two cancer outcomes.

6. Consideration of the Conclusions Related to DMA

The charge to the SAB (2007) was not limited to issues related to the *Toxicological Review*, but also included a review of a document addressing the carcinogenicity of dimethylarsinic acid (DMA^V). While these two assessments were critically reviewed simultaneously, the conclusions related to the potential carcinogenicity of DMA should be considered since DMA^V is a major metabolite of inorganic arsenic. The SAB (2007) was specifically asked to comment on how best to consider the pharmacokinetic processes in cancer risk assessment based on data for DMA versus direct inorganic arsenic exposure and to also comment on the assumption that "USEPA further expects that the tumorigenic profiles vary with the arsenical compound administered."

Posing these questions, and the SAB's response to these questions, clearly illustrates the lack of integrated consideration of all of the data and a lack of consideration of the available data for DMA to inform decisions related to the potential mode of action and carcinogenicity of inorganic arsenic.

- SAB (2007) noted that it is not surprising that administration of inorganic arsenic to rodents does not produce bladder tumors but administration of DMA does. This provides

evidence that DMA is the proximate bladder carcinogen. However, this conclusion is not considered in the current draft 2010 assessment for inorganic arsenic.

- USEPA apparently concurs and has proposed to use the DMA rat bladder tumor data to develop a cancer slope factor for human bladder cancer risk by extrapolation from the rat data. The USEPA has further stated that the mode of action for DMA in the rodent bladder is via a cytotoxic mode of action and that this cytotoxicity must be present before bladder tumors are seen. Therefore, the DMA mode of action is considered non-linear and in the absence of doses high enough to cause significant bladder cytotoxicity, unlikely to be a human carcinogen.

- In a discussion of the mode of action for arsenic-induced bladder cancer (page 99 of the *Toxicological Review*), it is proposed that after inorganic arsenic ingestion, DMA^{III} was excreted into the urine above a critical concentration, reacted with urothelial sulfhydral groups resulting in urothelial cytotoxicity and necrosis, thus leading to urothelial regenerative cell proliferation (hyperplasia) and urothelial cancer.

    - This mode of action is identical to that presumed for the rat, and therefore, is also a non-linear process with a threshold.
    - The extrapolated human cancer slope factor (CSF) derived from the rat data for DMA should be compared to that derived from the epidemiological data to provide bounds to the analyses of the epidemiological data.

The conclusions from the review of DMA are clearly inconsistent with the conclusions regarding the mode of action for inorganic arsenic. This demonstrates a lack of integration in the current *Toxicological Review* of the available information for arsenic compounds in the determination of cancer potential from exposure to inorganic arsenic in drinking water.

7. Consideration of the MOA for Inorganic Arsenic

In the current *Toxicological Review*, linear extrapolation is applied for dose-response modeling due to an unknown MOA. However, the draft does discuss that for the proximate metabolite of inorganic arsenic, DMA, bladder cancer (endpoint of concern for inorganic arsenic) may occur by a nonlinear MOA. Results from recent epidemiological studies suggest the presence of nonlinearities in the dose-response curve, with no observed increased risk of bladder, lung, and liver cancer risk following chronic exposure to low concentrations (<100 ppb) of inorganic arsenic via drinking water (Chen et al. 2009, 2010; Guo 2003; Ferreccio et al. 2000; Baastrup et al. 2008; Bates et al. 1995; Steinmaus et al. 2003; Lamm et al. 2004; Meliker et al. 2007; Lamm et al. 2007). Further, several studies applied a control or referent group exposed to arsenic concentrations less than or equal to 10 µg/L (e.g., Chiou et al. 2001; Guo et al. 2001). Additionally, the *Toxicological Review* stated in the review of the Meliker et al. (2007) study that "the potential explanation for the lack of significant findings were the low levels of arsenic in the ground water of southeastern Michigan, which may be below the threshold for cancer induction and other moderating factors that were not considered by this study (i.e., food as a source of arsenic exposure)."

Recent ongoing collaborative research between The Hamner Institutes for Health Sciences, USEPA, ENVIRON International, and EPRI (see EPRI Comments Appendix A) continues to focus on development of a MOA for inorganic arsenic, including the following:

1) The refinement of physiologically based pharmacokinetic (PBPK) models of the kinetics of inorganic arsenic and its metabolites in the mouse and human;
2) The investigation of mathematical solutions for multi-stage cancer models involving multiple pathways of cell transformation;
3) The review and evaluation of the literature on the dose response for the genomic effects of arsenic; and,
4) The collection of data on the dose response for genomic changes in the urinary bladder (a human target tissue for arsenic carcinogenesis) associated with *in vivo* drinking water exposures in the mouse, as well as *in vitro* exposures of both mouse and human cells.

Results of this research include multiple peer-reviewed publications (see earlier list within Introduction), with the most recent being a review of the dose-response data for genomic effects of arsenic (Gentry et al. 2010). This review demonstrated clear evidence of the concentration dependence of arsenic effects on the expression of various genes or proteins. Current genomics analyses in mouse and human bladder cell conducted as part of this project have also provided insights into the MOA for arsenic (Clewell et al. 2008; Yager et al. 2010).

Recently (January 2010), the initial results from much of the research effort, specifically genomics analyses in mouse and human bladder cells following arsenic administration, was reviewed by an external Science Review Panel (SRP). The conclusions of the SRP were that that significant progress had been made on research to support an arsenic MOA that could be used in risk assessment. They further concluded that the work by EPRI, as complemented by other research presented at the meeting, has provided important new insights into the molecular and cellular events associated with arsenic carcinogenicity and voiced in the meetings that current results were not suggestive of a linear mechanism. The SRP unanimously commended the researchers on their work as well as EPRI for funding such research (especially in light of the limited funding afforded to arsenic by other groups). Arsenic remains an important compound from an environmental health perspective and further research should be encouraged.

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

1. Intake Assumptions/ Sensitivity Analysis

Several critical assumptions were made in the modeling of the Taiwanese data, including assumptions regarding consumption of arsenic in both water and non-water sources that can have a significant impact on risk estimates for inorganic arsenic in U.S. populations. In the case of water consumption, SAB (2007) recommended a sensitivity analysis to examine the impact of using different water consumption values in Taiwan. SAB (2007) also questioned the source of Taiwan gender-specific intake/consumption values and recommended equal gender-specific

consumption, and further stated that documentation of the source of data on water consumption in Taiwan was needed as well as the source of data for intake from other beverages and cooking water.

Additional SAB (2007) recommendations related to water consumption that have not been addressed in the February 2010 *Toxicological Review* are as follows:

- All water consumption values for both U.S. and Taiwan populations were changed from the previous model; however, the reasons for these changes are not apparent (Table 5-7, USEPA 2010)
- Gender-specific water consumption values for Taiwan were maintained against the recommendations of SAB
- Lack of clarity in how different sources of water intake were incorporated into the risk model including beverages other than water (e.g. green tea) and water used in food preparation.
- Sources for the current intake values are not provided.

While sensitivity analyses have been conducted to examine the impact of some of the assumptions applied in the dose-response analysis, as well as assumptions related to non-water intake of arsenic, the analyses conducted to date remain simplistic. While they demonstrate limited impact on the estimated CSFs (with the exception of female bladder cancer), interactions between some of the parameters that were examined would be expected anyway, and no combinations of endpoints were explored in the *Toxicological Review* in these analyses. Interactions between the parameters could exhibit different results from what might be obtained by varying the parameters individually while holding all other parameters fixed. Specifically, the impact of (and sensitivity to) the choice of a quadratic function for the dose-response analysis; the impact of (and sensitivity to) that choice might have turned out very different under different assumptions, including the amount of water consumed, well arsenic concentrations, and non-water source values with the quadratic model.

The impact of the selection of a referent population on the low-dose region of the dose-response curve is not discussed. Based on the results of the sensitivity analysis, this assumption can have a significant impact on the estimation of the URs associated with bladder cancer (Tables 5-10, 5-11, USEPA 2010). This is likely attributed to the lack of information for the low-dose region from the Taiwanese data, with the data from the referent population having the largest impact on this region of the dose-response curve.

In addition, several aspects of the sensitivity analyses themselves are unclear, as the input data used for the model are not provided, nor is the Excel workbook with the Solver analysis. The SAB (2007) recommended that "all tables of inputs for these models be published in appendices to the Issue Paper or final risk assessment so that reviewers can independently reference and verify the critical inputs to the hazard and excess risk analysis." However, there was no attempt to provide documentation adequate for duplicating the sensitivity analyses conducted for the *Toxicological Review* (USEPA 2010).

2. Non-water Arsenic Intake

One of the critical assumptions in the *Toxicological Review* is the estimate of non-water intake of inorganic arsenic. It is currently assumed in the *Toxicological Review* that non-water intake in both the referent and exposed populations were 10 µg of arsenic per day, presumably as inorganic arsenic. However, the literature from studies conducted in similar geographic and cultural areas of Asia suggests that the range of total arsenic in food intake values appears to be closer to 100-200 µg/day.

Inorganic arsenic comprises 30-85% of total arsenic in rice –a staple food in Taiwan. In U.S. rice, inorganic arsenic levels are about 0.1 mg/kg, while DMA in rice increases linearly with increasing total As (Zavala et al. 2008). Given the predominance of rice in the diet of the Taiwanese population, the assumption that reference groups, with either zero or extremely low arsenic concentrations in groundwater, had the same daily non-water arsenic intake as the exposed population is not supported by the data. When rice was cooked in groundwater containing high concentrations of arsenic, the arsenic content in that rice was 5 to 17 times as high as in rice cooked in water with no arsenic or low concentrations of arsenic (Laparra et al. 2005). In addition, it is critical to note that rice cultivated in groundwater with high arsenic concentrations, but cooked in arsenic-free water, still retained high concentrations of arsenic, mainly in the form of DMA (Juhasz et al. 2006).

Lack of a consideration of this difference in arsenic content from rice, a staple in the Taiwanese diet, would result in an underestimate of the total arsenic intake in the exposed population and an overestimate of the potency of arsenic in the development of cancer, in particular bladder cancer. Finally, to assume that not considering non-water sources of arsenic would bias any study toward the null is just that – an assumption. To cite non-U.S. populations, such as that in Bangladesh, for this assumption within the *Toxicological Review* appears invalid for U.S. populations.

In conducting sensitivity analyses related to non-water arsenic intake, using the same value for intake in both the referent and exposed population assumes the same food source of arsenic in both populations. While other assumptions may have been investigated, it is not clear from the documentation of the sensitivity analyses what the non-water intake of inorganic arsenic in the reference population was when the exposed population had values of 1, 100 and 200 µg/day applied. However, specific variations in the amount in the control population *versus* water-exposed population should have been explored.

It is important to note that USEPA conducted a sensitivity analysis of the impact of the assumption of 50-200 µg/day from non-water intake and demonstrated that 100-200 µg/day produced the most stable CSF results particularly for risk of bladder cancer in Taiwanese females (USEPA 2008, Table 5-6). Regardless of these results, in the derivation of the recommended CSF, it appears that the USEPA (2008) relied upon the default value of 10 µg/day arsenic in food for both Taiwan and U.S. population as the base case value. The rationale supporting this final value used is not clear. However, USEPA justified the use of 10 µg/day for the Taiwan reference population by stating that non-water arsenic intake greater than 50 µg/day for populations outside the exposed area (which is approximately five times the typical non-water arsenic intake in the U.S.) was not considered credible. However, this statement belies the fact that SAB (2007;

Section 3.5.5) cited three recent independent studies of dietary arsenic intake in Bangladesh and West Bengal (areas of high naturally occurring arsenic) (Chowdhury et al. 2001; Watanabe et al., 2004; Roychowdhury et al. 2002) showing total arsenic values in food ranging from 120 – 285 µg/day.

The recommendation from the SAB (2007) was to assess background arsenic intake values in the exposed Taiwanese population from 50 µg/day up to at least 200 µg/day. When proportional changes in cancer risks are evaluated for non-water arsenic intake input assumptions in the exposed Taiwanese population of 100 µg/day and 200 µg/day as recommended by SAB (2007), estimated cancer risk for male and female lung and bladder cancer risk *decrease* by 5 to 20% (*Toxicological Review*, Tables 5-8 and 5-9). The proportionate decrease in estimated cancer risk across the cancer types and sexes appears to be stable. Given available data on total and inorganic arsenic levels and intake values for non-water sources in Taiwan and especially for rice (Schoof et al. 1998; Lin et al.2004; DOH, Taiwan, 2009), and the determination that 50-60% (EFSA, 2009) or even 30-85% (Zavala et al. 2008) of total arsenic in rice is inorganic arsenic plus the known reliance on rice as a food staple in this region, the assumption of 10 µg/day of non-water arsenic intake appears excessively low for this population.

Figure 5-2 in the *Toxicological Review* (February 2010) shows the proportionate changes in risk when risk estimates increase as a result of changing input assumptions, but this figure fails to include those instances where estimated cancer risk is *decreased*. Selectively choosing data from the sensitivity analysis for Figure 5-2 that solely supports increased risk while failing to incorporate those sensitivity analysis outcomes that show decreased risk is inappropriate and misleading. Transparency would be enhanced by plotting all data from Table 5-9 in the Figure 5-2 histogram.

With regard to female bladder cancer, it appears that cancer risk estimates are most stable when non-water arsenic intake for the exposed population is assumed to be 200 µg/day. Since female bladder cancer risk estimates in the Taiwan study population appear to be unstable under most scenarios with the above-noted exception, it would be of benefit to critically compare results with other epidemiology studies to determine if there is consistency and coherence for specific cancer outcomes at various arsenic drinking water levels for females. This analysis is important in order to assess whether the Taiwan database is yielding anomalous results with regard to female bladder cancer risk. For example, a cursory examination of results from nine bladder cancer studies (Chiou et al. 2001; Bates et al. 1995; Kurttio et al. 1999; Steinmaus 2003; Karagas et al. 2004; Bates et al. 2004; Michaud 2004; and Baastrup et al. 2008) indicates that not one of them report an increased risk for bladder cancer in females compared with males and all studies found a significant effect on bladder cancer risk associated with smoking. Thus, the Taiwan database yields results not seen in eight other well-conducted epidemiology studies. This inspection does not engender high confidence in the choice of the Taiwan study population to derive bladder cancer risk estimates relevant to the U.S. population.

Summary

EPRI respectfully requests that the SAB Workgroup consider the questions ands issues raised in this comment document. Scientifically justified alternative assumptions and modeling approaches to those used in the current draft of the *Toxicological Review* (USEPA 2010) will have a significant impact on the estimation of the potential risk to human health following exposure to low concentrations of arsenic compounds. EPRI has provided information from epidemiological studies not currently considered in the *Toxicological Review,* as well as identifying questions and concerns with the current draft assessment. Although organized relative to the SAB Workgroup charge questions, these comments focus on several main points for consideration:

- As recommended by the SAB (2007), a critical review of all arsenic epidemiological drinking water studies has not been conducted that uniformly apply specific criteria to each individual study.
- Because a uniform set of criteria have not been transparently applied in the draft *Toxicological Review*, several important epidemiological studies have been removed from consideration for quantitative assessment, limiting the information available to characterize the low-dose region of the dose-response curve.
- Epidemiological studies, including studies from the Taiwanese populations (Chen et al. 2009; 2010), more recent than those using for dose-response modeling (Chen et al. 1988, 1992; Wu et al. 1989) are available in the peer-reviewed literature that can provide additional information needed to characterize the shape of the dose-response curve in the low-dose region. These studies also demonstrate a lack of effect at drinking water concentrations of <100 ppb.
- Additional information is still needed to support many of the assumptions and approaches incorporated in the dose-response assessment of the *Toxicological Review*. These include:
    - the continued reliance on older Taiwanese studies when newer analyses of this population are available (Chen et al. 2009; 2010);
    - additional evaluation to characterize the exposure-response information from the Taiwanese studies;
    - an attempt to integrate the available data from low-dose studies for dose-response analyses;
    - consideration of a cumulative dose metric for use in the dose-response assessment;
    - the method for combining unit risk estimates;
    - the potential impact of smoking; and,
    - consideration of the SAB conclusions as related to DMA carcinogenicity and mode of action, and particularly how those may impact conclusions provided in the *Toxicological Review*.
- Although a sensitivity analysis was conducted, the draft *Toxicological Review* lacks adequate discussion on the potential impact of the assumptions applied, such as the referent population and non-water intake of arsenic, capable of influencing the cancer unit risk estimate.

As discussed above, it is EPRI's intent to: 1) provide these data and raise these questions as the SAB Workgroup evaluates the wealth of data on these complex issues; and, 2) assist the SAB

Workgroup in the integration of these data. As such, the final *Toxicological Review* will reflect the state-of-the-science, and be recognized by all stakeholders as scientifically defensible.

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Table 1. Uniform Comparison of Study Characteristics for Selected Cancer Epidemiology Studies

Design Study Population Reference	Outcome Definition	Population size	Smoking status	Arsenic Exposure	Results	Evaluation on Uniform Criteria[a]	Comments
Cohort Prospective Denmark Baastrup et al., 2008	Incident primary lung cancer	Population 57,503 (n= 402 lung cancer cases)	Personal interview- 35% Never smokers 29 % Past smokers 36% Current smokers	Exposure range: 0.05 to 25.3 ug/L (mean = 1.2 µg/L) 99th percentile of TWA exposure = 5.7 µg/L	IRR[b] (95% CI) Adjusted Analysis TWA Exposure IRR: 0.99 (0.92-1.07) p-value: 0.78 Cum. Exposure IRR: 1.0 (0.98-1.02) p-value: 0.80	1.Exposure misclassification likely low due to use of exceptional municipal records and GIS methods 2. Very low reliance on imputed exposure levels 3. See Previous Column 4. Participation rate: 57,053 persons out of 160,725 invited 5. Exposure variability was minimized by calculating both TWA and cumulative arsenic concentration for each individual taking into account all sequential residential addresses for that individual 6.Control selection not applicable to prospective study design. 7. Coherence of results with other studies for this range of arsenic concentrations is reasonable (see Lewis et al, 1999; Ferreccio et al., 2000, Smith et al. 2009; Chen et al., 2004; Mostafa et al. 2008; Chen et al. 2009; Han et al., 2009.	No significant interaction between arsenic and smoking was seen. IRR estimates for never, former, and current smokers were not significantly different for cancers of the lung or bladder (both p > 0.12). Narrow confidence intervals on incidence rate ratios indicating good precision.
Cohort Prospective Northeastern Taiwan Chen, et al., 2009	Incident lung cancer	Population 6,888 (n= 178 lung cancer cases)	Personal interview- 59% Never smokers	Average conc. in well water (ug/L) < 10	Multivariate-Adjusted RR (95% CI) 1.00	1. Low degree of exposure misclassification due to individual well water	No apparent increase for lung cancer risk observed between 10 and 100 µg/L. Increased risk for squamous cell and small cell

			12.4 % Past smokers 28.6 % Current smokers	10-49.9 50-99.9 100-299.9 ≥ 300	1.00 (0.65-1.57) 1.14 (0.62 – 2.11) 1.34 (0.73-2.43) 2.65 (1.56- 4.48)	arsenic concentrations being measured on the entire cohort. 2. Low extent of reliance on imputed exposure levels 3. 53% of cohort exposed to < 1000 µg/L-years cumulative exposure 4. Participation rate excellent. Recruitment from 4,586 households of 18 villages 5. Arsenic analyses were conducted on water samples collected from individual wells that the 6,888 cohort participants used. 6. Control selection not applicable to this study design 7. Coherence of results with other studies in same exposure range is good (see above).	carcinoma lung cancer (but not adenocarcinoma) between 100 and 300 µg/L (RR= 2.25 (1.43-3.53).Personal interview included smoking history and information to estimate latency, recency and cumulative arsenic exposure. Increased risk for smokers with increasing arsenic concentration, but not for non-smokers.
Cohort Prospective Northeastern Taiwan Chen et al., 2010	Incident urinary cancer[b]	Population 8,086 (n = 45 cancer cases)	Determined by personal interview; data not given	Average conc. in well water (ug/L) < 10 10-49.9 50-99.9 100-299.9 ≥ 300 Unknown	% Pop. RR[c] (95% CI) 28.3 1.00 25.9 1.70 (0.56-5.19) 11.2 2.49 (0.72-8.59) 11.2 4.18 (1.37-12.8) 8.6 7.73 (2.69-22.3) 14.8 3.10 (1.01-9.48)	1. Unable to identify exposure level in fifteen percent of cohort; exposure misclassification low in remainder of cohort since determined by individual water arsenic concentrations being measured as well as personal interview for residential history, etc. 2. Extent of reliance on imputed exposure levels is low 3. Number of persons exposed at each exposure level yields reasonable distribution across the exposure gradient (see previous column) 4. Participation rate	For exposures < 100 µg/L, cancer risk was elevated but not significant. $P_{trend} < 0.001$. There were 79,433 person-years at risk among the subjects for whom arsenic concentration in well water was measured. Relatively wide confidence intervals on RR estimates.

						high. Recruitment of 8,086 residents from 4,586 households of 18 villages 5. Arsenic concentrations analyzed on 3,901 water samples collected from 4,584 households (85.1%). 6. Control selection not applicable to this study design 7. Coherence of results with other studies in same exposure range is good (see above).	
Cohort Prospective Denmark Baastrup et al., 2008	Incident bladder cancer	Population 57,503 (n= 214 cancer cases)	Personal interview- 35% Never smokers 29 % Past smokers 36% Current smokers	Exposure range: 0.05 to 25.3 ug/L (mean = 1.2 µg/L) 99th percentile of TWA exposure = 5.7 µg/L	IRR[c] (95% CI) Adjusted Analysis <u>TWA Exposure</u> IRR[d]: 1.01 (0.93-1.11) p-value: 0.75 <u>Cum. Exposure</u> IRR: 1.0 (0.98-1.04) p-value: 0.55	1.Exposure misclassification low due to use of excellent municipal records and GIS methods 2. No or low reliance on imputed exposure levels 3. See Previous Column 4. Participation rate: 57,053 persons out of 160,725 invited 5. Exposure variability was minimized by calculating both TWA and cumulative arsenic concentration for each individual taking into account all sequential residential addresses for that individual 6.Control selection not applicable to prospective study design. 7. Coherence of results with other studies for this range of arsenic concentrations is reasonable (see above)	No significant interaction between arsenic and smoking was seen. IRR estimates for never, former, and current smokers were not significantly different for cancers of the lung or bladder (both p > 0.12). Narrow confidence intervals on incidence rate ratios indicating good precision.
Ecological Southwestern Taiwan Chen et al. (1992)	Lung and Bladder cancer mortality	Population size not reported (n = 304 lung cancer deaths; n = 202 bladder	Smoking status not reported	< 10 10-29 30-59 60 +	Males & females were reported separately. They had similar age-specific mortality rates from bladder cancer. Males had	1. Degree of exposure misclassification likely relatively high due to ecological study design. 2. Relatively high	Ecological study design presents multiple weaknesses compared with prospective design. Reliance on death certificates resulting in potential diagnostic

		cancer deaths)			a higher mortality from lung cancer than females at age > 50 but no consistent differences in lung cancer mortality were observed for younger age groups. Age and smoking adjusted mortality rates were not reported. Multistage models were used to calculate cancer potency indices.	reliance on imputed exposure levels. 3. Number of persons exposed at various estimated levels of drinking water arsenic not reported. Person-years by age, sex and arsenic level is reported. 4. Participation rate is not reported nor can it be inferred from the data presented. 5. No estimates of exposure variability presented, but likely relatively high due to unknown well water source(s) for any given individual. 6. Control selection not applicable to ecological study design. 7. Study displays coherence of findings relative to other studies of the Blackfoot Disease endemic region that consists of a small area (30 km by 40 km) in Southwestern Taiwan.	bias.
Ecological Study Southwest Taiwan Wu et al., 1989	Bladder and Lung Cancer Mortality (ICD-8)	174,945 9(?) (n = 181 bladder cancer cases) (n = 268 lung cancer cases)	Unknown	Low < 0.30 ppm Medium 0.30 – 0.59 ppm High ≥ 0.60 ppm	Age-adjusted mortality rate per 100,000 (n cases) <u>Bladder</u> *Males* *Females* Low 22.6 (23) 25.6 (30) Med. 61.0(36) 57.0(36) High 92.7(26) 111.3 (30) <u>Lung</u> *Males* *Females* Low 49.2 (53) 36.7(43) Med. 100.7 (62) 60.8(40) High 104.1(32) 122.2(38) $P_{trend} < 0.001$	1. Potentially high degree of exposure misclassification due to ecologic study design and other well documented factors 2. High reliance on imputed exposure levels 3. Number of persons exposed at each exposure level is not presented. 898,806 total person-years are reported for all ages, sexes, and arsenic concentrations for 1973-1986. 4. Participation rate not	Ecological study design presents multiple weaknesses compared with prospective design. Reliance on death certificates resulting in potential diagnostic bias. Risks reported for females not replicated in studies of other geographic locations by other investigators.

						presented therefore unknown. 5. No estimate of exposure variability presented; likely relatively high due to unknown well water source(s) for any given individual. 6. Control selection not applicable to ecological study design. 7. Study displays coherence of findings relative to other studies of the Blackfoot Disease endemic region that consists of a small area (30 km by 40 km) in Southwestern Taiwan.	

[a]Uniform Evaluation Criteria (SAB, 2007):

1. Degree of exposure misclassification
2. Extent of reliance on imputed exposure levels
3. Number of persons exposed at various estimated levels of drinking water arsenic
4. Study response/participation rates
5. Estimates of exposure variability
6. Control selection methods in case-control studies (Not applicable to prospective studies).
7. Coherence of study findings with other studies in similar exposure range

[b]Includes urothelial carcinoma(formerly called transitional cell carcinoma (bladder), non-urothelial carcinoma, and urinary cancer in renal pelvis
[c]RR is Relative Risk
[d]IRR is Incidence Rate Ratio

Appendix A

Memorandum of Understanding

(Provided as a Separate PDF file)

PALO ALTO OFFICE
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MEMORANDUM OF UNDERSTANDING

between

CIIT Centers for Health Research ("CIIT")

and the

United States Environmental Protection Agency
Office of Research and Development
Environmental Protection Agency
National Health and Environmental Effects Research Laboratory
("NHEERL")

and the

Electric Power Research Institute
Environment Division
("EPRI")

PURPOSE AND SCOPE OF MOU:

The purpose of this MOU is to document the relationship between CIIT, NHEERL and EPRI (hereinafter each may be individually referred to as "Researcher" or collectively as the "Researchers"), and to outline each of their roles to achieve the Goal (as defined below). This MOU encourages the Researchers to transfer amongst each other information regarding arsenic mechanistic modeling. Each Researcher will contribute to this effort through appropriate means including, but not limited to, program coordination, exchange of information, and the sharing of other relevant expertise.

This MOU is strictly for internal management purposes for each of the Researchers. It does not create a legally binding obligation and shall not be construed to create any legal obligation on the part of either Researcher.

This MOU shall not be construed to provide a private right or cause of action for or by any person or entity; specifically, failure by any of the Researchers to complete their respective roles and objectives shall not allow any of the other Researchers to bring any legal claims for recovery.

This MOU shall not be used to obligate or commit funds of any Researcher, or as the basis for the transfer of any Researcher's funds.

This MOU in no way restricts either of the Researchers from participating in any activity with other public or private agencies, organizations, or individuals.

This MOU is neither a fiscal nor a funds obligation document. Nothing in this MOU authorizes or is intended to obligate the Researchers, either now or in the future, to expend, exchange, or reimburse funds, services, or supplies, or transfer or receive anything of value,.

GOAL:

The Goal is to have the Researchers cooperate, collaborate and utilize their respective expertise and capabilities in order to: 1) advance the state-of-the-science for arsenic mechanistic modeling, and 2) develop and apply a human pharmacokinetic model and pharmacodynamic modeling approaches for arsenical compounds.

INTRODUCTION AND BACKGROUND:

The Researchers are conducting similar research activities on the application of computational methods and cutting edge molecular biology tools to characterize the hazard identification and dose response assessment of important environmental contaminants. During the preceding several years, EPRI and NHEERL have each separately supported development of pharmacokinetic ("PBPK") models for arsenic. EPRI has developed both human and mouse PBPK models while NHEERL has developed a mouse model. Arsenic is a contaminant for which multi-media, multi-pathway exposures and both cancer and non-cancer health effects are of concern. EPRI's principal interest in arsenic is as a component of coal fly ash to which both ambient and occupational exposure may occur. A portion of the current effort by all three Researchers is devoted to improving the scientific basis upon which risk assessments are built. It is this area of research that would benefit from closer coordination and collaborative efforts. The research programs and missions of each Researcher are very complementary, providing an excellent mix of expertise and interests for collaboration in this type of activity.

CONTRIBUTIONS TO AND ROLES FOR THE MUTUAL PROJECT:

This mutual project nicely compliments work currently being undertaken by EPRI to refine older published arsenic models developed under its sponsorship and will link NHEERL's pharmacokinetic modeling efforts with EPRI's and CIIT's interest in pharmacodynamic modeling. This mutual project is expected to provide all Researchers access to additional data and expertise in order to more quickly and efficiently advance overall modeling efforts.

In addition to jointly developing the new human pharmacokinetic and pharmacodynamic model, the Researchers are expected to jointly apply the model to biologically-based low dose cancer and non-cancer risk assessments across different exposure doses and exposure routes.

EPRI's Role

EPRI developed a human pharmacokinetic model that encompasses intake from all routes of exposure but does not incorporate extensive mode of action information nor tissue dosimetry for the various forms of arsenic and arsenic metabolites. These data and their incorporation into the model are critical to realistic application of such a model to human health cancer risk estimates for low ambient exposures. In addition, EPRI has supported and continues to support a number of investigations into mode of action of low level exposure to arsenic species related to human DNA repair, oxidative damage, and methyltransferase kinetics, as well as lung inflammatory processes in order to fill "data gaps" for the human model. EPRI has also supported development and publication of an arsenic mouse PBPK model incorporating elements of tissue dosimetry.

EPRI is expected to provide the model definition file (not software source code) and documentation from the original Mann-Droz human research grade pharmacokinetic model, which is what the Researchers will use together with source model definition file NHEERL has developed for the research grade organoarsenical model, to develop a final research grade human inorganic arsenic pharmacokinetic model. EPRI is also expected to provide data on the metabolism of inorganic arsenic in primary mouse hepatocytes, data from studies on the interaction of arsenic metabolites with specific genes and proteins associated with cell replication and the response to oxidative stress.

CIIT's Role

CIIT is expected to bring its broad range of general expertise in the development of physiologically based pharmacokinetic and pharmacodynamic models, in the characterization of target tissue dosimetry, across species extrapolation tools and its systems biology approaches. CIIT laboratories are expected to be available for toxicogenomic studies as well as other ancillary studies to complement the modeling work.

Depending upon CIIT priorities, CIIT is expected to:

(1) permit NHEERL and EPRI personnel to assist in studies conducted by CIIT on arsenicals of mutual interest and to be involved in training and educational opportunities;

(2) permit CIIT personnel to assist in studies conducted by NHEERL on arsenicals of mutual interest and to be involved in training and educational opportunities; and

(3) allow CIIT personnel to attend joint meetings with NHEERL and EPRI personnel to exchange pertinent data, coordinate and schedule research activities.

NHEERL's Role

The NHEERL research program brings considerable research experience and data specific to arsenicals. The NHEERL research program on arsenicals has focused thus far on cancer mechanism research, collection of pharmacokinetic data in mice to support the development of in vivo PBPK arsenical models, as well as development of subcellular and cellular models describing arsenic methylation using in vitro data on methylation mechanisms generated by NHEERL. NHEERL modeling efforts have addressed, in particular, issues concerning methylation mechanisms, lung accumulation and renal handling and excretion of the various arsenical compounds.

NHEERL is expected to contribute their experience and data regarding pharmacokinetics and pharmacodynamics, and the model definition files NHEERL has developed for the research grade organoarsenical pharmacokinetic model.

Depending on National Health and Environmental Effects Research Laboratory ("NHEERL") priorities, NHEERL is expected to:

(1) permit CIIT and EPRI personnel to assist in studies conducted by NHEERL on arsenicals of mutual interest and to be involved in training and educational opportunities;

(2) permit NHEERL personnel to assist in studies conducted by CIIT on arsenicals of mutual interest and to be involved in training and educational opportunities; and

(3) allow NHEERL personnel to attend joint meetings with CIIT and EPRI personnel to exchange pertinent data, coordinate and schedule research activities.

QUALITY ASSURANCE PROJECT PLAN:

Any research conducted under the auspices of this MOU would be subject to the Quality Management Systems and Quality Assurance Plans of the respective Researcher.

PUBLICATION:

All Researchers undertake this work with the intent to publish results in the public domain in scientific peer-reviewed publications. Each Researcher will confer and consult prior to any release or publication of data generated through jointly conducted research. Prior to submitting for outside review or journal submission any manuscript or document co-authored by staff from the three Researchers, each Researcher will be offered fourteen (14) days to review such proposed publication. A seven (7) day review period shall apply to submission of any co-authored abstracts. Under this arrangement all data and models would be published in the open scientific literature and the model definition file (but not

source code) and model description would be provided to interested parties upon request once published in the literature.

Each publication and/or resulting product of this mutual project will acknowledge and give appropriate credit to all the Researchers as contributors to such publication or resulting product.

LENGTH OF RELATIONSHIP:

It is expected that the relationship between the Researchers will last four (4) years from the date of this MOU. The length of the relationship may be shorter or longer than four (4) years depending on the Researchers ability to continue and fulfillment of the Goal.

TERMINATION:

If, at any time, any Researcher wishes to sever the relationship with the other Researchers and stop efforts for the Goal, then that Researcher will, as a courtesy, inform the others with 14 days notice. Such notice, or lack of notice, will not give any Researcher a private right or cause of action.

AMENDMENTS

Amendment to this Memorandum of Understanding may be made at any time during the period by mutual agreement of all parties.

EXCHANGE OF FUNDS

This Memorandum of Understanding does not involve the exchange of funds nor establishes any obligation on the part of any or all parties to make payment now or in the future.

POINTS OF CONTACT:

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ACKNOWLEDGED:

The Researchers acknowledge this MOU only expresses their intent to have a relationship as described in this MOU. Signatures or initials below do NOT create any legally binding obligations for the Researchers.

CIIT Centers for Health Research ("CIIT")

_____

Melvin E. Andersen, Director, Division of Computational Biology
Date: 9/29/2005

United States Environmental Protection Agency
Office of Research and Development
National Health and Environmental Protection Agency
Experiment Toxicology Division ("NHEERL")

_____

Linda S. Birnbaum, Director, Experimental Toxicology Division
Date: Sept 26, 2005

Electric Power Research Institute ("EPRI")

Dr. Terry Surles, VP, Environment Division
Date: 9/7/05