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These comments are submitted to the workgroup of the chartered Science Advisory Board that is conducting an expedited and focused review of EPA’s draft “Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)” (EPA/635/R–10/001) in accordance with the Federal Register Vol. 75, No. 39, March 1, 2010 notice.

The short timeframe allowed by EPA for this review has prevented completion of a detailed review of the EPA draft document by most commenters. It is also unlikely that the members of the SAB workgroup will have sufficient time to fully assess the EPA document, submitted comments and substantial recent literature that has not been cited by EPA.

As described in these and other comments, there are substantial flaws in EPA’s dose response analysis for inorganic arsenic that result in markedly overstated low dose risk estimates. EPA has not adequately responded to the recommendations of the SAB (2007) arsenic panel. The current SAB work group should recommend that EPA revise the dose response assessment to better respond to the SAB (2007) recommendations and to incorporate results of recently published studies, as well as ongoing EPA research programs. Although there are substantial potential economic impacts from a change in the arsenic cancer assessment, there are likely to be no public health benefits from increasing the oral slope factor. Risk-based drinking water standards are already far below natural background arsenic concentrations in surface water and groundwater. Similarly, default risk-based action levels for soil are far below natural soil arsenic concentrations around the world, and background dietary intakes of inorganic arsenic far exceed intakes from incidental soil ingestion. I urge the SAB work group to keep these facts in mind as they deliberate.

My comments focus on several issues related to Charge 3, specifically dietary intake of inorganic arsenic and water consumption rates. Brief comments are also provided on the other charges, in some cases cross referencing comments by other parties.
Comments addressing SAB Charge 1: Please comment on EPA’s response to the recommendations and the conclusions of the SAB (2007) arsenic panel regarding the evaluation of the epidemiological literature.

EPA has only partially responded 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. There are two primary issues relating to EPA’s evaluation of the epidemiological literature.

First, EPA has not adequately addressed limitations in the Taiwanese dataset and continues to ignore evidence that use of the median concentrations from the “low dose” villages may markedly underestimate exposures of people who developed cancer. EPA has also used an inappropriate Southwest Taiwan comparison population that has much lower cancer risk than the study population at the same water concentration. These points are discussed further in comments below on Charge 2.

Second, as described in detail in comments submitted by Exponent, EPA’s 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. As noted by Exponent, the current draft IRIS document is also not up-to-date with the epidemiologic literature published during the past 3 years (see Exponent’s comments for a list of these studies). Notably, Mink (2008) conducted a meta-analysis to examine the potential association between low-level exposure to arsenic in drinking water and bladder cancer. The summary relative risk estimate (SRRE) in the meta-analysis restricted to data from never-smokers was less than 1.0. The SRRE for analyses of never-smokers and ever-smokers combined was slightly but not significantly elevated. The database from low-exposure populations is growing and many of the issues that are raised in the draft IRIS document (EPA 2010) have been addressed in more recent, updated studies (e.g., Chen et al. 2009, 2010). EPA should update and re-evaluate the epidemiological literature for useable evidence of the dose response at low doses.
Comments addressing SAB Charge 2: Please comment on EPA’s response to the SAB’s recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.

EPA (2010) has failed to adequately address two major aspects of the SAB (2007) recommendations in modeling arsenic cancer risks. First, the mode of action (MOA) discussion isn’t grounded in a dose-response assessment that could yield insights to the relevance of observed responses to cancer risk, and second, the modeling used the Taiwanese dataset in ways that inappropriately characterize the low dose response.

EPA’s (2010) mode of action (MOA) discussion isn’t grounded in a dose-response assessment that could yield insights to the relevance of observed responses to cancer risk. EPA’s (2010) analysis of mode of action (MOA) is presented in Section 4.4.1. “Possible Modes of Action and Key Events of Possible Importance”, with detailed tables in Appendix C. EPA’s (2010) analysis based on likely MOA key events fails to make effective use of available data to describe the dose-response of arsenic effects on the expression of various genes and proteins, and the likely mode of action. As described by Gentry et al (2010, available online June 23, 2009) “[T]he available in vitro gene expression data, together with information on the metabolism and protein binding of arsenic compounds, provide evidence of a mode of action for inorganic arsenic carcinogenicity involving interactions with critical proteins, such as those involved in DNA repair, overlaid against a background of chemical stress, including proteotoxicity and depletion of nonprotein sulfhydryls. The inhibition of DNA repair under conditions of toxicity and proliferative pressure may compromise the ability of cells to maintain the integrity of their DNA”.

Gentry et al. (2010) reviewed 800 citations that identified genomic responses following in vivo or in vitro arsenic administration, and found 160 articles with arsenic concentrations specified. These studies yielded approximately 1,100 data points for a specific genomic-related response for some 354 specific genes or proteins. For in vitro studies in primary cells, this compilation of studies provided a clear picture of varying effects of arsenic at the lowest concentrations (below 0.1 µM) vs. responses at 0.1 µM to 10 µM or higher. Gentry et al. (2010) observed a concentration-related hierarchy of responses that began with changes in gene and protein expression associated with adaptive responses. Above 0.1 µM additional responses appeared associated with oxidative stress, proteotoxicity, inflammation and proliferative signaling. At concentrations above 10 µM changes in apoptotic genes were most prominent. This analysis provides additional support for a nonlinear mode of action and has informed ongoing in vivo studies on genomic alterations in mouse bladder that will inform efforts to extrapolate to human bladder carcinogenicity (Clewell et al. 2007, Clewell 2010, Kenyon et al. 2008a, 2008b).

EPA’s (2010) modeling used the Taiwanese dataset in ways that inappropriately characterize the low dose response. As described in comments by Exponent, Gradient and Dr. Lamm, EPA’s (2010) baseline model has three primary flaws: 1) use of an inappropriate comparison population, 2) exposure misclassification that classifies as low dose villages that included high concentration wells, and 3) the assumption that the comparison population had no arsenic in their drinking water.
The dose-response assessment presented in EPA (2010) 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. This comparison population includes 2 million people, overwhelming the influence of the less than 1,000 people in each of the 18 villages in the study area. As noted by Exponent, 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. One wonders if distortions introduced by use of an inappropriate comparison population are responsible for the nonsensical finding in the EPA sensitivity analysis that assuming higher background dietary arsenic intakes causes the slope factor to increase (see comments on charge 3 below).

EPA should not use the comparison population in their baseline analysis. EPA (2010) claims that use of the comparison population does not make much of a difference; however, as described by Exponent, whether or not a comparison population is used has less of an effect if a linear relationship is forced through the data.

Several studies have noted that a number of study area villages classified as low dose villages include high concentration wells. It is probable that for these villages, cancer risk is associated more closely with consumption of water from the high concentration wells than from the low concentration wells. EPA's reliance on the median concentrations to characterize exposures in these villages likely underestimates exposures. As noted by Exponent, 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. Brown (2007) found that 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. As recommended by Dr. Lamm, EPA should present the cancer risk analysis for the “low-exposure” villages defined as either that the mean village well arsenic level is less than 150 µg/L or that the maximum village well arsenic level is less than 150 µg/L.

EPA (2010) also assumed that the comparison population had no arsenic in their drinking water, which is contrary to available data and to technology. As described by Dr. Lamm the Southwest Taiwan region, like the study area, lies atop the Chianan plain [Lewis et al., 2007] and likely have the same drinking water sources. Chen et al. (1962) reported that the median arsenic level in non-endemic area shallow wells was 25 µg/L and non-endemic artesian wells was 380 µg/L. Chiang et al. (1988) reported that 45-54% of wells in non-endemic area had arsenic content greater than 50 µg/L and 0-6% greater than 350 µg/L. Uncertainty regarding exposures of the comparison population is another good reason not to use the comparison population.
Comments addressing SAB Charge 3: Please comment on EPA’s sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.

The following comments focus on the baseline values of non-water inorganic arsenic intake and water consumption assumed by EPA.

EPA (2010, Section 5.3.5 “Nonwater Arsenic Intake and Drinking Water Consumption”) does not consider numerous relevant references that support different baseline values for relative intakes of inorganic arsenic from dietary sources and consumption rates of drinking water in exposed and reference populations, and in the U.S. population.

Presumably, the purpose of EPA’s (2010) toxicological review is to provide a basis for quantifying the incremental risk of arsenic exposures from non-background sources in the U.S. Thus in using epidemiological data from exposed populations to derive a dose response assessment, an understanding of the relative intakes of inorganic arsenic from dietary sources and consumption rates of drinking water in exposed and reference populations, and in the U.S. population is important for understanding the incremental risk of arsenic exposures from non-background sources in the U.S. In this regard it is noteworthy that EPA ignores or misinterprets the literature cited in selecting the baseline values for dietary intake of inorganic arsenic and drinking water consumption rates and that the most recent primary scientific reference cited by EPA in support of their selected baseline values is dated 2001. In the intervening decade, substantial research has been conducted that supports values different than those selected by EPA. EPA (2010) also does not adequately address the SAB (2007) recommendations on these topics. These issues are discussed below for dietary intakes in Taiwan and in the U.S., and for water consumption in Taiwan.

Dietary inorganic arsenic intakes were substantially higher in Taiwan than assumed by EPA (2010). Despite citing Schoof et al. (1998) as supporting a Taiwanese dietary intake estimate of 50 µg/d, EPA (2010) states that they selected 10 µg/d as the best estimate of non-water arsenic intake for baseline calculations based on the available information”. It appears that EPA may have selected this value based on “studies of arsenic intake from countries where arsenic exposures are much lower than in Taiwan”. This section of the draft toxicological assessment and the EPA assumption are inconsistent with the literature. EPA’s assertion that “it is likely that the arsenic intake in non-endemic area (background arsenic intake value for the reference population) is lower than that reported in the endemic area” is also without foundation. Schoof et al. (1998) reported that soil arsenic concentrations were not elevated in areas where yams were collected; suggesting that high arsenic drinking well water had not affected fields from which the yam samples were collected. Subsequent studies of world-wide arsenic concentrations in rice (for example, Zavala et al. 2008, Meharg and Rahman 2003, Williams et al. 2006, Williams et al. 2007) are consistent with data reported by Schoof et al. (1998), and show that high rice consumption rates will be associated with high inorganic arsenic intake regardless of location. The estimate of Schoof et al. (1998) is also consistent with dietary intake studies conducted in other areas Southeast Asia. Notably, Kile et al. (2007) conducted a duplicate diet study in
Bangladesh and report average background dietary intake of 46 µg/d total arsenic (with 82% of total arsenic being inorganic arsenic) in areas without elevated drinking water arsenic. This study also demonstrated that as drinking water concentrations of arsenic drop below 50 µg/L, arsenic intakes become dominated by dietary arsenic intake (Kile et al. 2007). The implication of this finding is that once drinking water concentrations are 10 µg/L or less, there is effectively no further decline in arsenic intake with declines in drinking water arsenic concentration. Even higher intake estimates are provided by Ohno et al. (2007), but one third of the 18 families they studied used contaminated water for cooking. In conclusion, available literature indicates that EPA should use a baseline non-water inorganic arsenic intake in the range of 30-60 µg/d for the Taiwanese population. Furthermore, there is no basis to include intakes of 0-10 µg/d in the sensitivity analysis.

Non-water arsenic intake was addressed by the SAB (2007) in response to charge question D5: Charge Question D5 asks the SAB “…. what background dietary arsenic intake value it recommends for both the control population and study population of Southwestern Taiwan (which is used in deriving the cancer slope factor for inorganic arsenic)?”

**SAB (2007) Conclusions Based on Available Science**

- Assumptions of arsenic levels in food have a substantial impact on the assessment of risk from arsenic in drinking water.

**SAB (2007) Recommendations**

- No specific value to be used for dietary arsenic exposure was recommended.

- A sensitivity analysis to assess the impact of a range of dietary intakes on risk from lung cancer and bladder cancer associated with arsenic in drinking water should be conducted. The analysis should evaluate the impact of food intake values from at least 50–100 µg per day to perhaps 200 µg per day.

- It should not be assumed that the control population has an intake value of zero for arsenic from food.

- A more comprehensive discussion of data used in the assessment, including sources, methodological and analytical issues, and bioavailability should be included. Biases and relative strengths of assumptions should be discussed.

- The issue of arsenic bioavailability should be given immediate research attention.


In particular, EPA (2010) does not address the bioavailability of dietary arsenic. Evidence of high bioavailability is presented by Xue et al. (2010) who matched dietary intake estimates with urinary arsenic data. In a pilot study He and Zheng (2010) also
report proportional increases in urinary arsenic excretion after increasing dietary arsenic intake, suggesting high bioavailability. Juhasz et al. (2006) present evidence that close to 90% of inorganic arsenic in rice is absorbed.

**Dietary inorganic arsenic intakes are lower in the U.S. than in Southeast Asia.** Studies published during the past decade provide substantial information on dietary inorganic arsenic intakes both in the U.S. and in Southeast Asia. The benchmark study of intake of inorganic arsenic in the U.S. diet was conducted by Schoof et al. (1999), who reported an average daily inorganic arsenic intake of 3.2 µg/d, with a range from 1 to 20 µg/d. Other studies of North America and European populations that EPA has failed to consider include Yost, et al. (2004) who reported an average dietary inorganic arsenic intake in U.S. children of 3.2 µg/d (range 1.6-6.2 µg/d), and Baeyens, et al. (2009) who reported an average dietary inorganic arsenic intake for Belgian consumers of 5.8 µg/d. The most recent U.S. study, just published in March 2010 provides a probabilistic model of dietary arsenic exposure in the U.S. using 2003-2004 NHANES data (Xue, et al. 2010). This study estimated that the mean intake of inorganic arsenic from food in the U.S. is 1.96 µg/d. Although only recently published, this study was conducted by EPA scientists and partially funded by EPA. Since it was submitted to the journal in July 2009, presumably EPA scientists had access to this information prior to that time. **Taken together, these studies provide a much more robust understanding of U.S. background exposure to inorganic arsenic in the diet than acknowledged by EPA (2010), and document lower dietary intakes of inorganic arsenic compared to the Taiwanese study population.**

**Taiwanese drinking water consumption estimates are too low and should include water used for cooking.** EPA (2010) uses a baseline assumption that water intake is 3.5 L/day for males and 2.0 L/day for females. Barely a page of text is devoted to explaining the selection of these values, which mainly appears to be justified as being consistent with NRC (1999). In contrast, the studies cited by EPA consistently support higher consumption rates. EPA’s 1989 arsenic work group report estimated Taiwanese water consumption to be 4.5 L/day when cooking water was included, and EPA notes the arsenic rule (EPA 2001) assumed water consumption rates of 4.5 L/day for males and 3.5 L/day for females (including cooking water). EPA further notes that Chowdhury et al. (2001) support their baseline assumptions; however, the reported water consumption values of 4 L/day for males and 3 L/day for females are higher than EPA’s baseline assumptions and do not include cooking water intakes, which are estimated to be 1 L/day. More recent studies also support higher water consumption. The Bangladesh women studied by Kile et al. (2007) consumed an average of 2.7 L/day of water. Similarly, Watanabe et al. (2004) reported mean water consumption of 3 L/day for men and women.

While these studies report average consumption rates, drinking water consumption varies substantially among individuals with values as high as 6-10 L/day reported by Watanabe (2004). These high end consumers will receive greater arsenic doses and be at greater risk of developing cancer. Use of a central tendency estimate artificially reduces the highest doses and distorts the shape of the dose response curve.
Drinking water consumption was addressed by the SAB (2007) in response to charge question D4: Charge Question D4 asks, “[w]hat drinking water value does the panel recommend for use in deriving the cancer slope factor for inorganic arsenic?”

**SAB (2007) Conclusions Based on Available Science**

- Water consumption assumptions have a substantial impact on the assessment of arsenic’s risk.

**SAB (2007) Recommendations**

- No specific drinking water rates were recommended.

- EPA should evaluate the impact of drinking water consumption rates associated with more highly exposed population groups with potentially different exposures and susceptibilities (e.g. children, pregnant women) in its arsenic exposure estimates.

- Uncertainty and variability in the drinking water parameters for the Taiwanese study population should be explored. Specifically, EPA should:
  
  - Incorporate variability parameters for individual water consumption into the dose response analysis in the Taiwanese population as has been done for the U.S. population.
  
  - Conduct sensitivity analyses of the impact of using a range of consumption values for the Taiwanese population.

- Further justification and explanation of exposure assumptions is needed. Specifically, EPA should:
  
  - Provide better justification for the assumption of different drinking consumption levels by gender.
  
  - More fully discuss and completely document the source of data for intake from various sources of water.

EPA (2010) has failed to respond adequately to the SAB (2007) recommendations. In particular, it appears that EPA is not including cooking water in daily water consumption estimates and has not considered the impact of using average consumption rates instead of considering high end consumption rates. Based on available data, EPA’s baseline water consumption rates should include water used in cooking. The sensitivity analysis should include upper percentile water consumption rates due to the higher doses and greater risk faced by high end water consumers in the study population.

EPA’s (2010) sensitivity analyses should include combinations of multiple factors to accurately gauge the impacts of overly conservative assumptions. The sensitivity analysis should include an assessment of a combination of factors to fully assess the magnitude of uncertainty in the analysis. As noted earlier, the increase in the slope factor or risks for drinking water exposures at 10 µg/L when higher non-water
arsenic intakes are assumed seems illogical. One wonders if this outcome is indicative of a flaw in EPA’s dose response model. It seems possible that a sensitivity analysis with the higher non-water intakes could have a different effect if applied to the analysis without a reference group. Combining multiple varied assumptions in the sensitivity analysis would allow EPA to explore issues with model performance.

In trying to understand how the EPA model could have produced higher risk estimates as background non-water arsenic intake is increased, I asked Dr. Lorenz Rhomberg at Gradient for help. He found this outcome puzzling and offered the following very preliminary thoughts.

“The equation being used is Eq.5-2 (p.127), and a few lines after it (line 6, p.128) appears the model terms explanation, “In this model, the exponential term represents \( h0(t) \) in Equation 5-1. The age-dependent risk of cancer at the "background" doses of arsenic (zero from drinking water and 10 ug/day from diet in the preferred model). The last term in the equation captures the dependency of risk on the daily ingestion dose of arsenic.” In Eq. 5-1, \( h0(t) \) is "cancer mortality risk in the reference population at age t" and comparing 5-1 and 5-2, it is equal to the first term in 5-2, i.e., \( \exp(a1 + a2age +a3 age^2) \). The "last term" of 5-2 in the quote above (equivalent to \( g(x) \) in 5-1) is \( 1 – b(dose) \).

In other words, they are implicitly saying that "dose" in Eq. 5-2 is the WATER ingestion dose, since the diet dose is incorporated into the background term. If this is so, then the diet dose does not appear in the equation 5-2 at all as a separable entity. In this case, it is not clear how changing the diet dose changes the slope at all -- the diet dose is what it is, it leads to the observed cancer mortality in the background population, and it is only this observed mortality that enters the fitting of Eq. 5-2. It would be an error to add the diet dose to the "dose" term in fitting this equation, since this would effectively count the diet twice for the villagers exposed via water, once for their own diet and once for the allowance for the effect on mortality of that diet in the first term.

On the other hand, line 16 of p.128 says "The total arsenic dose received by the population of any village was estimated as the sum of the nonwater dietary intake plus the median arsenic well water concentration [times water consumption rates]." That is, "dose" in Eq 5-2 is the sum of diet and water doses, according to this. The ambiguity is enhanced by the switching of notation in the middle of Eq. 5-2, where dose = x on the left side and dose = "dose" on the right.

So, maybe EPA made an error and considered the background mortality \( H0(t) \) to include the diet dose when estimating that term, but then added diet into the "dose" term in the second term. But this would tend to make the slope "b" smaller rather than larger when one increases the diet contribution (since the same observed risk in villages would be attributed to a larger total dose, making the "b" shrink).

Another possibility is that line 6 on p.128 is just wrong – the \( H0(t) \) term is not for a referent population with only diet dose, it is for a hypothetical population with zero total dose. In this case, when fitting the model using a referent population, that population gets a non-zero dose (corresponding to diet) and the villages get the diet plus water doses, as described on line 16. That is, the reference population is just another positive dose point, albeit one with a large population and hence very influential in the curve fit. The slope "b" is then whatever value reconciles the curve fit to all the points, and the
mortality in the hypothetical zero-exposure population is found by extrapolating the curve to zero total dose, but there is no direct observation of such a zero-dose population and so the "age-only" first term of 5-2 is an extrapolation. If THIS is the case, then it is not clear how to apply to a US population, where there is no pure zero-dose age-only background mortality by which to multiply the effect of added arsenic.

But under this interpretation, there is a reason why the slope factors might be bigger with bigger dietary dose – with a bigger constant dietary component, the addition of 10 ug/L from water is a smaller proportional increment. For example, if the dietary contribution is 10 ug/kg and the water is 1 ug/kg, this is a 10% increment, but if diet is 100 ug/kg, the water is only a 1% increment. Given the multiplicative way that dose enters 5-2, a smaller increment from background to background+water yields a bigger value of "b" to give the same observed difference in risk in the curve fit.

The very fact that the sensitivity analyses show impacts of changing dietary exposure suggests that line 6 is indeed wrong and that the referent population is fitted with a positive dose equal to the dietary component alone. If this is so, then the method for applying this to a US background cancer risk becomes critical, since the US background has to allow for the US background arsenic exposure.”

Dr. Rhomberg did not have sufficient time to fully analyze these issues. In view of the critical nature of understanding the behavior of the EPA model, I urge the SAB to recommend that EPA fully explore and respond to this issue.

References


