As Arsenic Science Task Force

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Dear Dr. Orme-Zavaleta and Mr. Dunlap:

The Arsenic Science Task Force is grateful for the opportunity to express our concerns with the current plan for a revised IRIS assessment of inorganic arsenic. We are appreciative of the time afforded us at the February 5, 2020 meeting to elaborate on issues we had with the IRIS Assessment Plan and with its review by the NAS Committee. We hope the presentations by Drs. Cohen and Tsuji were helpful in understanding of our concerns. As promised, we are attaching an annotated version of the presentation.

Due to the limited time the meeting permitted, the expert presentations focused on two of the issues within the current trajectory of the IRIS assessment of inorganic arsenic: consideration of the well-established, biologically-grounded mode of action in evaluating the dose-response relationship, and the concerns regarding the inferences of dose-response relationships at low doses[1] from epidemiological studies dominated by high dose data, especially in light of the mode of action information and limitations of actual data at low doses in multiple epidemiology studies.

We found the discussion following our presentation to be very important, and reflective of the issues we had with the methods employed by the IRIS staff. We believe that the most important assertion made by the IRIS staff during the discussion --- *i.e.,* that **low dose data are now available** --- deserves a response. There are several issues with this statement as explained below:

[1] It is important to emphasize that there is no controversy about the potential impacts of exposure to very high levels of arsenic, such as occurring in certain populations relying on water with naturally occurring high levels of arsenic. In contrast, there is controversy with regard to whether low levels of arsenic cause effects. Low levels of arsenic are widespread and unavoidable in most natural sources of drinking water.

1) <u>The "low dose data" from epidemiological studies the IRIS staff claims to now be available, are from a few selected studies, or the results of modeling</u>

IRIS staff claims that –

> "…the database of epidemiological studies with exposures at lower doses has grown since 2013, making human study-based estimates for the dose-response curve in the lower range feasible" (NAS, 2019)[2]

This claim is misleading. The IRIS staff appears to be using data from just a few selected studies, ignoring the literature showing no effect at low doses. Furthermore, rather than considering a complete picture of the findings from epidemiological studies, as presented by Dr. Cohen and Dr. Tsuji, they use modeled data:

> "EPA has begun to implement several analytical approaches to utilize human data in the low-dose range and has introduced more advanced statistical methods in its dose-response evaluations that take into consideration human data from multiple studies. Some of these techniques are novel for the IRIS program…" (NAS, 2019)[2]

Once again, the IRIS staff asserts it is modeling dose-response at low doses. But data obtained by statistical modeling cannot substitute for actual data. When modeling effects of low exposures using statistical fitting across the full range of exposure, the upper end tends to drive the pooled cancer risks (Lynch et al. 2017). To avoid the influence of high exposure data on low exposure effects, the low exposure ranges should be analyzed separately. It is critically important that actual data that have not been manipulated be used for analyzing the low-dose response curve.

2) <u>Use of backwards calculations from physiologically based pharmacokinetics (PBPK)</u>

PBPK is often used for estimating tissue, blood or urine concentrations when exposure is known. IRIS utilized PBPK modeling to conduct a backwards calculation using total[3] arsenic levels in the urine from individuals surveyed in bladder cancer studies to estimate arsenic oral dose from drinking water. The backwards calculations assume that all the metabolites in tissues and in urinary excretion result from exposure to inorganic arsenic.

For inorganic arsenic, this approach is inappropriate because the same metabolites resulting from inorganic arsenic can also result from exposure to other arsenicals or to these compounds themselves. In 2014, Aylward *et al.*[4] examined urinary arsenic data from the National Health and Nutritional Survey (NHANES) 2009-2010 cycle and found association between urinary dimethyl arsenic acid (DMA) and monomethyl arsenic acid (MMA) with arsenobetaine. This association suggested either direct exposure to arsenobetaine from seafood sources, or metabolism of other organo-arsenicals to DMA and MMA. DMA in urine can also result from exposure to MMA and/or to DMA in food

[2] The National Academies of Sciences, Review of EPA's IRIS Assessment Plan for Inorganic Arsenic, 2019. Page 1

[3] Total arsenic – arsenic in any form

[4] Aylward, Lesa et al. (2014). Evaluation of Urinary Speciated Arsenic in NHANES: Issues in Interpretation in the Context of Potential Inorganic Arsenic Exposure. Regulatory Toxicology and Pharmacology, 69(1):49-54. doi: 10.1016/j.yrtph.2014.02.011.

(Cohen S.M. et al, 2006)[5]. Furthermore, the metabolism of arsenicals can differ between individuals, by age or by folate levels (Gamble et al. 2006, 2007)[6,7]. Using PBPK to calculate dose based on total arsenic compounds, or DMA in urine, produces exposure data that are inaccurate, and should not be used for assessing inorganic arsenic exposure.

3) Bias of study selection

Modelers usually favor datasets from studies displaying a positive dose-response that can be modeled. In fact, at the February 5 meeting the IRIS staff confirmed having used only epidemiological studies from which low exposure dose-response data could be calculated, indicating selection bias of studies and datasets within studies with positive dose-response that fit the models. Using only studies "that can be modeled" skews the results and leads to inaccurate conclusions of a dose-response relationship at low doses that simply don't exist.

It is also important to note that studies with negative results historically have not been published (Begum *et al.* 2015), which likely is one reason that studies of low exposure to inorganic arsenic are so scarce.

4) Exposure misclassification

IRIS (2019) and NAS (2019) appear to consider data from epidemiological studies as the best information source for the actual dose-response relationship at low doses, without recognizing the limitations of epidemiological studies for defining thresholds for effect levels. However, there are inherent weaknesses in many epidemiological studies, as Dr. Tsuji pointed out in her presentation. These weaknesses range from exposure misclassification to failure to account for confounding factors. Exposure characterization is a critical issue in epidemiological studies. For example, studies that assess exposure based on time-averaged or current drinking water arsenic levels, or doses, frequently do not accurately represent historical exposures, which may differ greatly from current exposures (Tsuji et al., 2019)[8]. Also, recall of exposure is a method used frequently for exposure assessment and has limitations. Individuals with cancer are usually inclined to recall an exaggerated exposure. Thus, recall bias is a factor that can skew the results and, in general, is a source of uncertainty and potential error.

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[5] Cohen, S.M., Arnold, L.L., Eldan, M., Lewis, A. and Beck, B. Methylated Arsenicals: The implications of metabolism and carcinogenicity studies in rodents to human risk assessment. Crit. Rev. Toxicol., 36:99-133, 2006

[6] Mary V Gamble et al. Folate and arsenic metabolism: a double-blind, placebo-controlled folic acid – supplementation trial in Bangladesh. Am J Clin Nutr. 2006 Nov; 84(5): 1093–1101.

[7] Mary V Gamble et al. Folic acid supplementation lowers blood arsenic. Am J Clin Nutr. 2007 Oct; 86(4): 1202-1209.

[8] Tsuji et al., Dose-response for assessing the cancer risk of inorganic arsenic in drinking water: the scientific basis for use of a threshold approach. Critical Reviews in Toxicology. 2019, DOI: 10.1080/10408444.2019.1573804

5) Ignoring data quality

In 1965, Sir Austin Bradford Hill published a list of fundamental criteria of causal inference in epidemiology, which are still used today (Fedak et al. 2015)[9] . One of these important criteria is *biological plausibility.* Researchers today put much more emphasis on the biologic basis for an association and have expanded the biological plausibility to the use of data from molecular biology, toxicology, genotoxicology and other disciplines. The current approach to the IRIS evaluation fatally ignores the need to demonstrate biological plausibility for the effects of low exposure to arsenic. Moreover, as presented by Tsuji in the February 5 meeting[10], as well as by Dr. Tsuji et al. 2019[8], the data IRIS was using for low doses did not show a statistically significant increase in risk.

In summary, IRIS should acknowledge the limitations and shortcomings of the proposed mathematical modeling approaches, which can lead to inaccurate estimates and wrong results. Instead, the IRIS assessment of inorganic arsenic should consider the mode of action (MOA) of inorganic arsenic and the actual nature of the findings in epidemiological studies at low doses. The 2013 NAS Committee strongly recommended that "[m]ode-of-action analyses should be used to inform dose-response modeling with respect to the shape of the curve, particularly in the low dose region…"[11]

IRIS staff has argued that MOA is not needed for two reasons: first, due to the ample availability of epidemiological data at low doses, and second there is no definitive MOA for inorganic arsenic. In this letter, we have shown that both arguments are wrong. First, the data at low doses from epidemiological studies demonstrate a lack of positive dose-response and little statistically significant association at low doses, and the modeled data fail to reflect the nature of these results. Second, the assertion by the IRIS staff that a mode-of-action argument needs to be definitive and exclusionary of any alternative approach before it can be presented as an informative analysis is incorrect. It is currently known that the MOA of cancer from exposure to inorganic arsenic is through binding to protein sulfhydryl groups, leading to cytotoxicity followed by cellular regeneration and cancer, as presented by Dr. Cohen at the February 5 meeting. This mechanism for cytotoxicity has a threshold for effects and hence, there is a threshold for cancer, *i.e.,* cancer risk would be absent without sufficient levels of cellular protein interference.

Importantly, as Drs. Cohen and Tsuji showed, there is a consistency of evidence from in vitro and in vivo studies on cellular concentrations that result in adverse effects. Both *in vitro* and *in vivo* effects occur when tissue level (or urine) reaches a level of 0.1 μM. In humans, to reach a tissue level of 0.1 μM, the oral dose has to be about 100 ppb in drinking water, calculated using very conservative assumptions. Importantly, epidemiology studies also support a threshold in humans of about 100 ppb in drinking water (Cohen, 2020[12]; Tsuji, 2020[13]).

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[9] Fedak, Kristen et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerging Themes in Epidemiology, 12:14, pages 1-9.

[10] Tsuji, JS, Presentation at the February 5 meeting, Slides Nos. 9-11 of Tsuji's presentation, (Nos. 28-30 of the attached presentation).

[11] The National Academies of Sciences, Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic. Interim Report, 2013. Page 6.

[12] Cohen, SM, Presentation at the February 5 meeting, Slide No. 18.

[13] Tsuji, JS, Presentation at the February 5 meeting, Slide No. 16 of Tsuji's presentation.

There are several other proposed MOAs, including reactive oxygen species (ROS) signaling and the oxidative stress that ensues, and perturbation of DNA methylation (Kitchin and Wallace, 2008[14]; Kitchin and Conolly, 2010[15]). It should be noted that most of the data for these other MOA's, especially regarding oxidative damage, are based on *in vitro* data at concentrations greater than 10 uM, a concentration which *in vivo* would be lethal. Nevertheless, all these other modes of action have thresholds at exposure levels consistent with the lack of observed increased cancer risk at the same low-dose range as in epidemiology studies of inorganic arsenic.

Finally, we reiterate our plea for disclosure of the evidence tables, and identification of those studies being most heavily relied upon in a timely fashion. We recognize that the normal course of action is to release the evidence tables concurrent with the posting of a draft IRIS assessment for public comment. However, we believe it would better serve IRIS and the public by providing the evidence tables prior to issuance of the draft assessment. The 2010 IRIS draft assessment of inorganic arsenic was roundly criticized for cutting off the review of the published literature prematurely. Other assessments have been criticized for studies selected, even after institution of systematic review. In particular, we know there are numerous epidemiology studies that claim to be low dose studies, when, in fact, they are not. The inorganic arsenic database is very large and greater transparency of the studies proposed to be relied upon is critical.

We hope that you and your team will give a thorough consideration of these concerns. A flawed assessment of this common naturally occurring element, which asserts a health risk to humans at low doses, will create enormous regulatory problems for the EPA program offices, the states and other stakeholders --- unnecessary problems since they are based on findings that are biologically implausible and scientifically unjustified.

Thank you again for your time and for your kind attention to the concerns raised in our meeting and further illuminated herein. We hope that we can find additional opportunities for continuing dialogue as the development of the draft proceeds.

Sincerely,

W. J. Adams

William J Adams, Ph.D.
ASTF Chairman

Attachment: ASTF annotated presentation

Cc: David Fischer, Deputy Assistant Administrator, OCSPP
ASTF members

[14] Kitchin, KT; Wallace, K. 2008. "The role of protein binding of trivalent arsenicals in arsenic carcinogenesis and toxicity." J. Inorg. Biochem. 102:532-539

[15] Kitchin, KT; Conolly, R. 2010. "Arsenic-induced carcinogenesis-oxidative stress as a possible mode of action and future research needs for more biologically based risk assessment." Chem. Res. Toxicol. 23(2):327-335.