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Submitted via email: wong.diana-m@epa.gov

September 30, 2024

Science Advisory Board
Inorganic Arsenic Review Panel
Dr. Diana Wong
Designated Federal Office
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Dr. Wong:

On September 17, 2024, the Science Advisory Board (SAB) released a Draft Report titled "Review of EPA's draft IRIS Toxicological Review of Inorganic Arsenic. The J.R. Simplot Company (Simplot) has provided extensive comments to EPA on EPA's Draft IRIS Toxicological Review of Inorganic Arsenic. This also included testifying and providing comments to the Science Advisory Board during the public hearing held in January 2024. We continue our engagement on this technical matter, which has significant regulatory and risk management implications, by providing comments on the SAB Draft Report on EPA's draft IRIS Toxicological Review of Inorganic Arsenic.

The J.R. Simplot Company (Simplot) is a privately held, global agribusiness organization headquartered in Boise, Idaho. The company is vertically integrated in the food supply chain, from mining phosphate ore to make fertilizers, to growing food and processing it, and finally to selling such products in the marketplace. IRIS assessments, such as the toxicological review of inorganic arsenic is of direct interest to Simplot because such assessments are used to develop water quality criteria, product quality and/or remediation targets relevant to our mining and fertilizer manufacturing operations.

As described in the attached comment document, which was written by scientists with Arcadis U.S. Inc., there are still significant concerns with the draft EPA IRIS Review. This includes that this toxicological review is based on a fundamentally new process to derive toxicological benchmarks. Such a significant change in how to derive toxicological benchmarks warrants extensive discussion and review as to if such a change is warranted and valid. The "results" of this toxicological review (i.e., the RfDs and CSFs) are values that exceed natural occurring (background) exposures in certain parts of the country. The use of these values in the establishment of regulatory criteria (such as surface water quality criterion or drinking water standards) has significant consequences the criteria set and the regulated community who has to meet these criteria.

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Please contact me at (208) 780-7365 if you have any questions about these comments.

Sincerely,

Alan L. Prouty
Vice President, Environmental & Regulatory Affairs

Attachment

C:
Dr. Paul D. Anderson Arcadis U.S. Incorporated
Dr. Norman D. Forsberg Arcadis U.S. Incorporated

IRIS Toxicological Review of Inorganic Arsenic (October 2023)

Comments on the Science Advisory Board's Draft Report, Titled "Review of EPA's Draft IRIS Toxicological Review of Inorganic Arsenic"

September 30, 2024

On September 17, 2024, the Science Advisory Board (SAB) released a Draft Report titled "Review of EPA's draft IRIS Toxicological Review of Inorganic Arsenic." USEPA specified that comments should be received by October 1, 2024. In these comments, the SAB's document is referred to as the Draft SAB Report (USEPA 2024). Inorganic arsenic is referred to iAs.

These comments focus on five general points as summarized in the bullets below and are discussed in greater detail in the remainder of this letter.

GENERAL COMMENTS

1. **<u>This SAB review is a great deal more than just a review of iAs toxicity. At its basis is a fundamentally new process to derive toxicological benchmarks (i.e., RfDs and CSFs.)</u>**

   One potential outcome of this new and potentially precedent setting process is the derivation of endpoint-specific reference doses for iAs that have no threshold for response. iAs is just the example compound. IRIS could apply this new process to many other substances. While elements of this novel process have been published individually in peer-reviewed journals (e.g., Allen et al. 2020a, Allen et al. 2020b, Hobbie et al. 2020), nowhere other than in the Draft iAs Toxicological Review, have all the elements been combined into a single problem-solving approach. To underscore the gravity of the situation, the Draft SAB Report notes that some decisions IRIS may need to make in response to the SAB's comments may "require that EPA make new science-policy decisions…"

   Before the novel dose-response and toxicity reference value setting approach that IRIS developed for the iAs assessment can be applied to any substance, including iAs, it requires full presentation in USEPA guidance separate from a review of the toxicity of iAs [much like is available in USEPA's guidance for benchmark dose modeling (2012), cancer risk assessment (2005), developing reference doses and reference concentrations (2002), and developing data-derived extrapolation factors (2014)] followed by in-depth critical expert review and public comment. This is consistent with concerns that SAB members discussed during the January 24-26, 2024 public meeting. Again, this should be wholly separate from a review of the toxicity of iAs.

2. **<u>The SAB review and its findings and conclusions fail to meet those expected of a critical review as, for example, are required of manuscripts submitted for publication in peer-reviewed journals.</u>**

The SAB notes several times in their draft report that it either did not have a sufficient amount of time to review all of the materials upon which IRIS' review was based or IRIS did not provide for the SAB's review data and papers excluded from the toxicological review. In light of these constraints on the SAB's review process, and notwithstanding the need for a separate critical review of guidance presenting the updated process for deriving IRIS toxicological benchmarks, another panel of experts (e.g., an SAB panel or perhaps the National Academies of Science) needs to review USEPA's responses to the SAB's draft recommendations and the revised IRIS toxicological review of iAs before IRIS finalizes the toxicological review for iAs.

3. **The SAB's classification of recommendations into three tiers deemphasizes several recommendations that are crucial to the accurate interpretation and application of updated toxicological benchmarks.**

The SAB has classified its recommendations into three Tiers of differing priority, with Tier 1 being the highest priority and generally needing an action or response from USEPA before finalizing the toxicological review while recommendations in lower Tiers are more along the lines of "would be nice to know but are not crucial." In several cases the outcome of recommendations classified as either Tier 2 or Tier 3 have the potential to change, potentially substantially, the toxicological benchmarks derived in IRIS' toxicological review. One such example is the SAB's Tier 2 suggestion to expand dose-response modeling sensitivity analyses to include models with a lower threshold effect for iAs exposure. The SAB made this comment in response to IRIS' decision to restrict their logistic model to achieve monotonicity and impose a lack of a lower threshold. Such recommendations should be classified as Tier 1, and completed and reviewed before the Draft IRIS Toxicological Review for iAs is finalized.

4. **Numerous SAB recommendations request added clarity regarding data, assumptions, and other aspects of the Draft Toxicological Review.**

It is not clear in many of those recommendations whether the SAB's request is simply to help IRIS improve the clarity of presentation, or if the SAB made these recommendations because they too needed clarification from USEPA so that the SAB could fully understand USEPA's methods and assumptions. At the January 24-26, 2024 public meeting, SAB members appeared genuinely confused about some of the dose-response modeling information presented by IRIS and asked USEPA to present the approach in person during the meeting. The Draft SAB report still indicates that IRIS needs to provide additional clarification on this topic. Hence, it seems like the SAB also needs more information to truly understand what IRIS did in the iAs review.

The SAB and USEPA must distinguish between recommendations that simply request editorial clarity versus those where the SAB itself needs more clarity to evaluate aspects of the Draft Toxicological Review. If a recommendation is related to the SAB's needing further information to fully understand and evaluate the information presented in IRIS' Draft Toxicological Review, then USEPA must provide that clarity to the SAB and the SAB should be allowed to determine if the findings of IRIS' review can remain or should be changed.

5. **The Draft SAB Report alludes to some of the practical implications of the updated iAs toxicity benchmarks, but not what to do about them.**

   For example, the SAB recommends that IRIS put the estimated background risks into perspective relative to USEPA's allowable cancer risk range. While we understand that the SAB's charge and role does not include commenting on risk management, to its credit, the SAB has recognized that the toxicological benchmarks presented in the Draft IRIS review would lead one to conclude cancer and non-cancer risks from everyday background exposure to iAs are much greater than previously thought and lead to substantial exceedance of USEPA's allowable risk targets in just by living in certain parts of the United States. Additionally, the SAB has questioned the scientific justification of deriving RfDs for iAs given that the novel modeling methods that IRIS employed (i.e., based on meta-regression, lifetable calculations, and subsequent model fitting to excess lifetime risk estimates using constrained modeling assumptions) show mathematically that any exposure to iAs is associated with extra risk (even if this is wholly inconsistent with the basic tenant of toxicology that "dose makes the poison"). The SAB raises similar practical concerns about IRIS' draft CSF because its use would indicate that exposure to naturally occurring background levels of iAs in food and drinking water would yield risk assessment estimates that exceed "the cancer risk range usually considered by EPA in developing health-based criteria." Concurrent with finalizing and releasing the IRIS toxicological review, USEPA needs to provide direction to risk managers charged with setting allowable concentration limits in soil, water, air, fish and other produce, on how to implement the new benchmarks and communicate the implications to the public.

DETAILED COMMENTS

I. The SAB generally supports the draft IRIS report, yet acknowledges a lack of sufficient time, resources, and guidance to perform a thorough review

The SAB appears to believe that much of the information reported in IRIS' Draft Toxicological Review of iAs generally is scientifically justified, but yet acknowledges that they did not have sufficient time or resources to perform a detailed review of the information that IRIS used to reach its conclusions. In total, the SAB was faced with reviewing 264 pages for the main report, 315 pages of the supplemental information, considering hundreds of references, and reviewing hundreds of modeling files (that were shared late with the SAB and with poor documentation). The SAB spoke directly to this point in their response to Charge Question 2a:

> "There is an incredible wealth of studies in HAWC and the committee members felt they did not have sufficient time to review many of the individual studies to appreciate whether the EPA approach and protocol was appropriate. Reviewers found it difficult to review the numerous papers that were excluded."

In response to Charge Question 2b, the Draft SAB Report states:

> "Although there was clarity and consistency for studies meeting high or medium confidence criteria, it was difficult to delve into the numerous papers that were excluded

> given the time allotted. EPA should provide more details about the specific metrics used to discount studies from consideration."

In response to Charge Question 4b, the Draft SAB Report states:

> "It appears that not all pertinent results from studies identified as relevant via EPA's systematic review were included in the quantitative meta-analyses. It was unclear why cited studies were excluded from the meta-analyses."

Additionally, several members of the SAB shared during the January 25, 2024 public meeting that they were unfamiliar with the meta-regression and lifetable calculations that IRIS employed for their dose-response assessment. The SAB members went so far as discussing whether the SAB should recommend IRIS develop guidance for these novel methods, similar to the guidance that exists for USEPA's benchmark dose modeling software.

Given these shortcomings, it would have been more forthright for the SAB to report that they did not have the time, resources, or guidance to properly peer-review the scientific defensibility of IRIS' draft toxicological review (similar to what is commonly done during the usual peer-review process for science publications if a peer reviewer cannot devote sufficient time and resources to properly complete a review). However, the SAB did not do this. Instead, they generally applauded IRIS and provided "advice" for ways IRIS could "enhance the transparency and increase the utility of the IRIS document." In light of these shortcomings in the scientific review process, the SAB or perhaps that National Academies of Science should be provided an opportunity to review IRIS' responses to the SAB's draft recommendations and the revised IRIS toxicological review before IRIS finalizes the toxicological review for iAs to comment on the document's scientific defensibility.

II. Tier 1 vs Tier 2 vs Tier 3 recommendations

The Draft SAB Report provides recommendations using the following Tiered categories:

- Tier 1: "*Recommended Revision* – Key major recommendations necessary for strengthening the scientific basis..."
- Tier 2: *Suggestions* – Recommendations that are encouraged to strengthen the scientific analysis and conclusions…"
- Tier 3: "*Future Considerations* – Scientific exploration that might inform future work."

The SAB made several "suggestions" that could directly affect the conclusions of the IRIS assessment. It is unclear if the SAB made these "suggestions" simply to help IRIS improve the clarity of presentation, or if the SAB made them because they too needed clarification from IRIS so that the SAB could complete their review properly. The SAB indicated that several of these critical "suggestions" were not of sufficient concern to warrant identifying them as Tier 1 recommendations. We disagree and recommend that IRIS treat the following of the SAB's "suggestions" as Tier 1 recommendations and provide either the SAB or the National Academies of Science an opportunity to review and comment on IRIS' response before IRIS finalizes the toxicological review for iAs.

a. Charge Question 2b – Tier 2 recommendation that should be Tier 1:

   i. "The report needs clarification on the key confounders, covariates, and risk modifiers and how these were incorporated into the assessment and synthesis."
   ii. "Although there was clarity and consistency for studies meeting high or medium confidence criteria, EPA should provide more details about the specific metrics used to discount studies from consideration"

b. Charge Question 3d – Tier 3 recommendation that should be Tier 1:
   i. "Mechanistic Observations (P3-120 L1): This section does not portray the current literature on iAs MOA. For example, the highlighted citation Herrera et al. (2013) used relatively blunt methodology at extremely high exposure levels (50 mg/L GD1-LD21) to achieve a measurable response. Additional studies are cited that also use very high exposure levels to implicate changes of glucocorticoid receptor and draw parallels to endocrine effects reported by Wasserman (2007). EPA should consider more recent MOA/AOP studies performed at doses and concentration much more relevant to human exposures in the U.S. (e.g., Niño 2019)."

c. Charge Question 4a – Tier 2 recommendation that should be Tier 1:
   i. "Review studies identified as relevant (included in hazard identification, but not meta-analysis) to confirm the absence of usable associations presented in Supplementary Materials for those papers."

d. Charge Question 4b – Tier 2 recommendations that should be Tier 1:
   i. "The dose conversion equations in the text, tables, and elsewhere (e.g., EXCEL files) need to be reviewed and corrected. The text currently describes the equations for cumulative drinking water exposure in mg/L*years and daily dose in mg/day but could be expanded to specify equations for the other metrics used including water concentration in mg/L and cumulative exposure in mg."
   ii. "All the calculation spreadsheets should be reviewed as an additional QA/QC step to ensure they are correct, and the terminology is consistent between the documents and the spreadsheets in light of the numerous editorial comments made on the document."
   iii. "Expand sensitivity analyses to include models with a lower threshold effect for iAs exposure."
   iv. "Examine differences between participant characteristics in the studies included in the meta-regression and the target population for the assessment. If differences exist, perform an analysis examining the impact of demographic factors on study-specific slopes."
   v. "When multiple studies from the same population are included in the same meta-regression model, examine the impact of the population on the overall slope by re-running the analysis with these studies excluded."
   vi. "Clearly describe the minimal data standards required for the meta-regression, including the minimum number of studies needed."

e. Question 4c – Tier 2 recommendations that should be Tier 1:
   i. "Perform sensitivity analyses removing the positivity restriction on the prior for the overall mean slope."

f. Charge Question 5a – Tier 2 recommendation that should be Tier 1:
    i. "Provide more details in the supplementary materials on how the lifetable calculations were performed, including a worked example and an explanation of required modifications when age-specific incidence rates are not available. The explanation should be comprehensible to a diverse scientific audience."
    ii. "Remark on the possible differences by country if a relevant U.S. reference for lifetime risk cannot be identified
g. Charge Question 6 – Tier 2 recommendations that should be Tier 1:
    i. "The approach used to account for background exposures in the lifetable analyses should be clearly presented, and the document should discuss that the estimated "background" cancer risks (from dietary exposure, with no additional exposure from drinking water) are much higher than the cancer risk range of 1 in 10,000 to 1 in 1,000,000 usually used by EPA."
    ii. "Consider adding discussion of how uncertainties related to systematic bias, residual bias, and uncontrolled confounding were considered for each outcome."
h. Charge Question 7a – Tier 2 recommendation that should be Tier 1:
    i. "Additional information should be provided about the rationale for exclusion of the 52 studies of neurodevelopmental behavioral effects considered (except for Wasserman et al. (2004) and Wasserman et al. (2014)). This discussion should include which criteria were not met for each excluded study. It should also discuss whether the two studies selected for dose-response analyses were the most sensitive and/or where the magnitude of the effects reported in those two studies fell relative to the overall evidence base."
i. Charge Question 8a – Tier 2 recommendations that should be Tier 1:
    i. "The novel use of sensitivity analyses requires more detailed discussion of how sensitivity/variability is considered in selection of UFH."
    ii. "To the extent possible, better utilize the systematic review process and findings to support data-driven selection and application of uncertainty factors."
j. Charge Question 9 – Tier 2 recommendation that should be Tier 1
    i. "The discussion of how background exposure was considered in the analyses presented in the draft document should be expanded, including a clear presentation of the information needed for application of the assessment's conclusions."

III. Practical Implications

a. The SAB Draft Report states that IRIS' draft CSF for bladder and lung cancer yields a combined risk of 1 in 1000 based solely on background dietary exposure and by 2 in 1000 based combined background dietary and drinking water exposure. As noted in our December 15, 2023 comments, similar conclusions would be reached. Additionally, the SAB has questioned the scientific defensibility of deriving a RfD for non-cancer effects given that the USEPA's novel modelling approach (i.e., based on meta-regression, lifetable calculations, and subsequent model fitting to excess

lifetime risk estimates using constrained modeling assumptions) show mathematically that any exposure to iAs is associated with extra non-cancer risk (even if this is wholly inconsistent with the basic tenant of toxicology that "dose makes the poison"). The fundamental error in USEPA's modeling approach that leads to these issues is their assumption that it is appropriate to use constrained models that yield only positive slopes for endpoints that they have concluded are causally related to iAs exposure. "Causal" is not a synonym for "liner dose-response curve" nor for "lacking a threshold." For these reasons, the SAB recommended that USEPA provide a clear presentation on how background exposure was considered in the dose-response analyses and provide "a clear presentation of the information needed for application of the assessment's conclusions." We agree that this is of paramount importance to ensure that whatever toxicity reference values IRIS ends up developing are useful from a practical standpoint. Once again, we refer you to the J.R. Simplot Company's December 15, 2023 comments, specifically sections V, VI and IX-XII. Those sections discuss the substantial shortcomings of the proposed RfDs and CSFs and demonstrate that adoption of those RfDs and CSFs will lead to estimates of risk that significantly exceed commonly used acceptable risk targets and would, therefore, be considered by USEPA to unacceptable due solely to naturally occurring conditions in large parts of the country. As a result, use of these proposed toxicity factors will have significant consequences for the establishment of regulatory criteria.

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AUTHOR BIOGRAPHIES:

Dr. Norman Forsberg: Dr. Forsberg has 13+ years of experience in toxicology and risk assessment. During this time, Dr. Forsberg has scoped and performed risk assessment projects for a wide range of industrial and governmental clients and provided technical review for projects in which the critical evaluation of toxicological data is key. He is experienced performing multimedia, multichemical, and multipathway risk assessments for federal and state superfund and RCRA sites across the United States, including decommissioned military sites, active and former chemical manufacturing sites, and mining sites. He has developed reference toxicity values and/or risk-based criteria for several classes of industrial and anthropogenic chemicals, including chlorinated and nonchlorinated solvents, per- and polyfluoroalkyl substances (PFAS), active pharmaceutical ingredients, metals, and PAHs. He also applies toxicological and risk assessment principles to support clients facing product stewardship-oriented problems, such as those associated with California's Proposition 65, OSHA HazCom, REACH, and TSCA. Furthermore, Dr. Forsberg is experienced at developing and validating analytical methods for organic and inorganic chemicals in a wide range of sample matrices using several analytical platforms. Dr. Forsberg has spent an extensive amount of time reviewing IRIS' draft toxicological review of inorganic arsenic and has participated IRIS' review process for inorganic arsenic via submission of comments to the public docket.

Dr. Paul Anderson: Dr. Anderson has almost 40 years of experience in human health and ecological risk assessment. He has been involved in evaluating the potential effects of pharmaceuticals in the environment as well as constituents of emerging concern (CECs). His work has also included investigation and assessment of PAH in sediments and a substantial amount of work on the assessment of human health and ecological risks posed by dioxins/furans, pharmaceuticals and metals. Dr. Anderson has performed numerous multimedia, multichemical and multipathway risk assessments for federal and state superfund sites throughout the United States including operating and abandoned chemical and manufacturing facilities, landfills, former wood treating sites, and pulp and paper mills. Dr. Anderson has managed the development of a watershed-based model that predicts environmental concentrations of pharmaceuticals and related compounds in United States surface waters. Dr. Anderson has served as a national expert on several Science Advisory Panels established by the California State Water Resources Control Board to provide recommendations for monitoring of CECs in recycled water and surface water. In addition, he has conducted human health and ecological risk assessments in support of the air and water permitting required for large industrial facilities and has prepared comments on the scientific basis of many Federal and State regulations such as the Great Lakes Water Quality Initiative, Federal and State Ambient Water Quality Criteria and derivation of human health and ecological toxicity benchmarks. Much of this work has been at sites and facilities where extensive negotiations with regulatory agencies have been critical for the successful completion of projects. Dr. Anderson is a leading advocate of advanced risk assessment techniques such as Monte Carlo analysis, has written over 30 papers and lectured widely on ecological and human health risk assessment, and has testified throughout the United States on the potential risks posed by dioxin and other chemicals. For more than 25 years Dr. Anderson was an Adjunct Assistant Professor in the Department of Earth and Environment at Boston University.