

**USDA Scientific Peer Reviewer's from USDA
Comments on Interagency Science Consultation
Draft IRIS Toxicological Review of Inorganic Arsenic
November 2022
(Date Received January 6, 2023)**

Peer reviewers from various USDA¹ agencies provide the following scientific comments for U.S. EPA's consideration.

Systematic Review Methods and Documentation

Tier 1 Comments: Recommended Revisions

- Reliance on Epidemiology Data with Limited Consideration for Mode of Action Data
 - Some reviewers had concerns about the reliance on epidemiology data in the absence of fully considering the available mode of action (MOA) data. Extensive MOA data are available for inorganic arsenic; however, these data were not fully considered in determining the candidate RfD values for inorganic arsenic. For example, Figure 2-1 (pg. 34) in the IRIS Toxicological Review of Inorganic Arsenic indicates that 982 MOA studies were identified through the initial database search and updates through 2015. Although Appendix A of Appendix A includes a brief discussion of some MOA data, the toxicological review focused on the use of epidemiological studies for dose-response analyses, which may have both high and low levels of arsenic exposure.
 - The draft IRIS assessment has considered only some of the total body of available information on the hazard of inorganic arsenic. Some reviewers recommend that IRIS provide a thorough review of the available MOA data and a discussion of how the MOA data compares to the epidemiology results. This additional information and rationale would scientifically strengthen the IRIS assessment.
 - Some reviewers expressed concern that interpretation of epidemiological studies is made more difficult without consideration of MOA information. When taken at face value, epidemiological data can mask issues related to averaging of high and low exposures, historical exposures of the same population, and exposure from other sources. These issues are difficult to disentangle without an understanding of the MOA.

¹ The USDA offices participating in the interagency scientific peer review include: the Food and Nutrition Service, Center for Nutrition Policy and Promotion; the Food Safety and Inspection Service, Office of Public Health Science; the Office of the Chief Economist, Office of Risk Assessment and Cost-Benefit Analysis; and the Office of the Chief Economist, Office of Pest Management Policy.

Tier 2 Comments: Suggestions

- Some reviewers had concerns that a literature review protocol was not created prior to the literature search, which is a standard practice for systematic reviews. A discussion of potential scientific impacts of the any changes in criteria over time would be beneficial for transparency purposes.

General comments in response to questions:

- The presentation and analysis of the epidemiology study results was clear and discussed risks of bias, study sensitivity, consistency, magnitude of effect and dose response evidence outlined in the report.
- Reviewers found risk of bias was assessed, and overall study ratings were clearly displayed and accounted for in the interpretation of the epidemiology evidence. The conclusions focus on evidence from medium or high confidence studies, and the effect potential bias in individual studies may have on health effects was considered in each synthesis.
- In discussing its estimates of excess cancers, U.S. EPA states that it multiplied the 95th percentile risk estimate by the lifetime exposure to estimate the lifetime extra risk for the endpoint in question. This is not technically correct. The resulting estimate is of the 95th percentile risk at that level of exposure. Using a shorthand that does not acknowledge the conservative nature of the estimate can be confusing and can increase the perceived level of risk posed by exposure to inorganic arsenic. Some reviewers suggest that when excess cancer risks are discussed, it should be clear that they are upper bound estimates.

Noncancer Hazard Identification

General comments in response to questions:

- Epidemiological studies assessing incidence of diabetes mellitus frequently use this term interchangeable with Type 2 diabetes. Assessment methods used are consistent with methods to assess type 2 diabetes. Consider eliminating reference to Type 1 diabetes.
- Presentation and analysis of study results is clear. Synthesis of evidence from human epidemiological studies support strength of evidence judgements. Judgements are transparent and accurately reflects risk of bias, study sensitivity, consistency, magnitude of effect and dose response evidence outlined in the report.

Additional Comments

Tier 3: Future Considerations

- **Consistency Within U.S. EPA**
 - USDA encourages scientific consistency across U.S. EPA.
 - USDA notes that U.S. EPA's Office of Pesticide Programs (OPP) has received a petition to review the carcinogenic mode of action and cancer classification for monosodium methanearsonate (MSMA), an organic arsenical herbicide. USDA encourages U.S. EPA to ensure that the outcomes of these two documents are aligned.

- The results of the cancer reclassification and the IRIS review may impact pesticidal uses of monosodium methanearsonate (MSMA).
- **Clarity and Scientific Impact**
 - A plain language explanation of how and why the proposed candidate RfD values differ from the existing RfD values, including a plain language explanation of the basis for the existing values, would be beneficial to aid the public in understanding the change, especially considering the potential impacts of the updated assessment.