Executive Office of the President (EOP)
Comments on the Interagency Science Consultation
Draft IRIS Toxicological Review of Inorganic Arsenic
November 2022
(Date Received December 21, 2022)

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of Inorganic Arsenic. We appreciate the comprehensive assessment and the careful consideration of epidemiological evidence bases is appreciated, including the acknowledgement and inclusion of tables around modifying factors. We have the following comments and clarifying questions on sections throughout the text:

- In the executive summary, the health effects paragraphs would read better starting with the overall conclusion of evidence demonstrates, and then say that the conclusion was based on robust body of evidence. This is in line with previous IRIS assessments, and similar to how it is presented in the Database Overview sections in Chapter 3.2. Or even as it is worded at the start of the "evidence judgement" part.

- Please define DCS at first use in the executive summary.

- There are some issues with citations being repeated or not formatted correctly (see page 3-11 for example). More broadly, there were some editorial issues throughout. Please ensure these are corrected prior to posting publicly (e.g., page 4-1, line 18-20)

- Please clarify on the comment around considering diabetes, pregnancy outcomes, and neurodevelopmental effects for further analysis based on cost-benefit concerns? Since IRIS is a non-regulatory program, what is the justification for this? Especially considering pregnancy outcomes and neurodevelopmental effects did not have as strong of an evidence base.

- "In summary, for this assessment, EPA evaluated multiple dose-response methods, including applying individual models to facilitate prioritization for more complex analyses and applying multiple traditional and Bayesian model-averaging and meta-regression methods to more fully utilize a wider array of studies for derivation of risk estimates." Is there any concern that by looking through so many analyses, model fit could be found by chance alone? (i.e., 5% of all models would fit by chance alone with a p-value of 0.05 – is this a concern since it seems like EPA ran a lot of models?)

- Why was diabetes considered for higher-level dose-response analysis? On page 4-3, it says that figure 4-1 justifies including diabetes, but it is not clear what the rationale was.

- On page 4-56 line 6, We recommend that EPA indicates that it was non-monotonic with the largest effect at the lowest exposure group.

- On page 4-55 line 10, EPA excluded the 2014 study in Bangladesh (W et al), but uses the study as a comparator. We suggest omitting the clause and explain that "The authors used a multiple linear regression analysis..."

- In the neurodevelopment section, please provide more context regarding how EPA interpreted the lack of D/R. Please explain how this conclusion was made, and expound on the reasoning. If there is not an explain, please consider excluding the endpoint.