FINAL External Peer Review Charge Questions for the IRIS Toxicological Review of Inorganic Arsenic

January 2024

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of the draft *IRIS Toxicological Review of Inorganic Arsenic* developed in support of the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's Center for Public Health and Environmental Assessment within the Office of Research and Development. IRIS assessments contain information about hazard identification and dose-response assessment, two of the four steps in the human health risk assessment process. When used by risk managers in combination with information on human exposure and other considerations, IRIS assessments support the Agency's regulatory activities and decisions to protect public health.

The previous *IRIS Health Hazard Assessment for Inorganic Arsenic* was completed and published in 1988 and included an oral reference dose (RfD) (last updated in 1991) for effects other than cancer, a determination of carcinogenic potential and an oral slope factor (OSF) (last updated in 1995). The draft *IRIS Toxicological Review of Inorganic Arsenic* is based on a comprehensive review of the available scientific literature on the noncancer and cancer health effects in humans exposed to inorganic arsenic (iAs). An *Updated Problem Formulation and Systematic Review Protocol for the IRIS Inorganic Arsenic Assessment* was released for public comment and review by the National Academy of Sciences, Engineering, and Medicine (NASEM) in May 2019; the NASEM report was published in October 2019 (NAS, 2019). The systematic review protocol for inorganic arsenic and other appendices for toxicokinetic information, dose-response modeling, and other supporting materials are provided as *Supplemental Information* (see Appendices A to E) to the draft Toxicological Review.

Charge Questions on the Draft IRIS Toxicological Review of Inorganic Arsenic

In response to the numbered charge questions below organized by topic area (italicized headers), the advice provided as part of this peer review would be most useful when prioritized to indicate its relative importance as follows:

- Tier 1: *Recommended Revisions* – Key major recommendations necessary for strengthening the scientific basis for the IRIS Toxicological Review of Inorganic Arsenic. The implication of such key Tier 1 recommendations is that the assessment conclusions are not adequately supported without addressing the recommendations and need to be reconsidered or better substantiated. For Tier 1 recommendations, please describe the specific revisions necessary to modify or better substantiate the most scientifically appropriate assessment conclusions.
- Tier 2: *Suggestions* – Recommendations that are encouraged to strengthen the scientific analyses and conclusions in the IRIS Toxicological Review of Inorganic Arsenic. It is understood that other factors (e.g., timeliness) may also be considered before deciding to address and/or incorporate Tier 2 suggestions. For Tier 2 recommendations, please provide

specific suggestions to strengthen the scientific basis for assessment conclusions or improve the clarity of the analyses and presentation.

- Tier 3: *Future Considerations* – Scientific exploration that might inform future work. These recommendations are outside the immediate scope or needs of the current document under review but could inform future Toxicological Reviews or research efforts.

Systematic Review Methods and Documentation

1. The IRIS Toxicological Review of Inorganic Arsenic describes and applies a systematic review protocol for identifying and screening pertinent studies. The protocol is described in brief detail in Section 1.5.1 (*Literature Searching and Screening*) and in full detail in Appendix A (Updated Problem Formulation and *Protocol for Inorganic Arsenic IRIS Assessment)*. If applicable, please identify additional peer-reviewed studies of inorganic arsenic that the assessment should incorporate[1].

2. As recommended in the 2019 NASEM review of the Inorganic Arsenic protocol, bladder cancer and lung cancer were accepted as hazards and only considered for the ability to update dose-response analyses. Similarly, the following health outcomes were included for evaluation of both hazard and, as appropriate, dose-response analyses: diseases of the circulatory system, diabetes, pregnancy outcomes, and developmental neurotoxicity. For these latter health effects, the Toxicological Review provides an overview of individual study evaluations, and the results of those evaluations are made available in the Health Assessment Workplace Collaborative linked here HAWC. Note that a "HAWC FAQ for assessment readers" document, linked here (scroll to the bottom of the page, and the document is available for download under "attachments"), is intended to help the reviewer navigate this on-line resource.

    a. Please comment on whether the study confidence conclusions for the Inorganic Arsenic studies are scientifically justified and clearly described, considering the important methodological features of the assessed outcomes. Please indicate any study confidence conclusions that are not justified and explain any alternative study evaluation decisions.

    b. Results from individual inorganic arsenic studies are presented and synthesized in the health outcomes sections. Please comment on whether the presentation and analysis of study results are clear, appropriate, and effective to allow for scientifically supported syntheses of the findings across sets of studies.

Noncancer Hazard Identification

[1] Newly identified studies (i.e., studies identified by EPA or the public that meet PECO criteria but were not addressed in the external review draft, for example due to recent publication) will be characterized by EPA and presented to the peer review panel. This characterization will focus on EPA's judgment of whether the studies would have a material impact on the conclusions (i.e., identified hazards or toxicity values) in the external review draft. The peer review panel is asked to review EPA's characterization and provide tiered recommendations to EPA regarding which studies, if any, to incorporate into the assessment before finalizing as well as their expected impact.

3. For each health effect prioritized for hazard identification in the assessment based on the protocol for inorganic arsenic and outlined below, please comment on whether the available epidemiological data (the primary focus of these analyses based on recommendations from the NASEM) have been clearly and appropriately synthesized to describe the strengths and limitations. Please also comment on whether the weight-of-evidence decisions for hazard identification are scientifically justified and clearly described, and appropriately consider health effects in susceptible subpopulations or lifestages (e.g., children) to the extent possible, given the available data.

    a. For diseases of the circulatory system, the Toxicological Review concludes the currently available ***evidence demonstrates*** that inorganic arsenic causes cardiovascular effects in humans given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <10 μg/L to 930 μg/L showing increased ischemic heart disease and hypertension, as well as related cardiovascular disease endpoints of atherosclerosis and repolarization abnormalities (e.g., QT prolongation).

    b. For diabetes, the Toxicological Review concludes the currently available ***evidence demonstrates*** that inorganic arsenic causes diabetes in humans given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <150 μg/L to >150 μg/L showing increased incidence of diabetes mellitus (Type 1 and Type 2 diabetes).

    c. For pregnancy and birth outcomes, the Toxicological Review concludes the currently available ***evidence indicates*** that inorganic arsenic likely causes pregnancy and birth effects in humans given sufficient exposure conditions. This moderate epidemiology evidence generally supports a weaker hazard judgment, although the specific judgment reached is more heavily influenced by other lines of evidence than when there is robust epidemiological evidence. Although there is notable uncertainty in this judgment without reviewing the other lines of evidence (out of scope for this assessment), it is reasonable to judge that the available evidence indicates that pregnancy and birth effects are likely caused by iAs exposure, given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <100 μg/L to >100 μg/L showing decreased fetal and post-natal growth or length of gestation.

    d. For neurodevelopmental effects, the Toxicological Review concludes the currently available ***evidence indicates*** that inorganic arsenic likely causes neurodevelopmental effects in humans given sufficient exposure conditions. This moderate epidemiology evidence generally supports a weaker hazard judgment, although the specific judgment reached is more heavily influenced by other lines of evidence than when there is robust epidemiological evidence. Although there is notable uncertainty in this judgment without reviewing the other lines of evidence (out of scope for this assessment), it is reasonable to judge that the available evidence indicates that neurodevelopmental effects are likely caused by iAs exposure, given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <100 μg/L showing cognitive and behavioral deficits in children and adolescents.

Meta-regression Analyses

4. EPA performed dose-response meta-analyses, herein referred to as meta-regression (MR) analyses on bladder cancer, lung cancer, diseases of the circulatory system (DCS), and diabetes and presents the results of these analyses in Section 4.3.

    a. Please comment on whether the application of a MR analysis and methods used to select studies for the MRs are clearly described and scientifically justified. If there are additional publicly available studies that warrant consideration as the basis of these analyses, please identify those studies, and outline the rationale for including them in the assessment.

    b. Please comment on whether the modeling approaches for the MR analyses, including calculation of effective counts, estimation of iAs intake values that account for background oral and dietary exposures, the choice of logistic regression for modeling response probabilities, and hierarchical Bayesian methods to estimate pooled slopes of the relationship between extra risk and dose, are scientifically justified and clearly described.

    c. In applying the hierarchical Bayesian model, EPA selected priors for the pooled MR slope such that the pooled slope could not be negative, reflecting the causal determinations for bladder cancer, lung cancer, diseases of the circulatory system, and diabetes. Please comment on whether this decision is scientifically justified and scientifically justified and clearly described.

5. EPA applied lifetable analyses to extrapolate estimates of MR pooled slopes to the desired target population (i.e., general United State population). EPA provides the results of the lifetable analysis as extra risk values calculated for a set of discrete iAs intake values, as well as polynomial trend lines with equations for the extra risk curves so that users can calculate extra risk values for each outcome at any dose they require. For each outcome below, please comment on whether the lifetable methods have been scientifically justified and clearly described.

    a. The Toxicological Review estimates extra risks at various iAs doses for multiple DCS endpoints: cardiovascular disease (CVD) incidence, fatal CVD, ischemic heart disease (IHD) incidence, and fatal IHD. Age stratified mortality values were available for fatal CVD and fatal IHD and were used in the lifetable analysis. Age-stratified DCS morbidity values were not available, and a single lifetime background risk value was used in the analyses for CVD and IHD incidence. At 0.13 μg/kg-day, a lifetime extra risk for CVD incidence of 2.1×10^{-2} was estimated.

    b. The Toxicological Review estimates extra risks at various iAs doses for type II diabetes mellitus. Age-stratified diabetes mortality and morbidity values were not available, and a single lifetime background risk value was used in the analysis. At 0.13 μg/kg-day, a lifetime extra risk for diabetes of 1.8×10^{-2} was estimated.

    c. The Toxicological Review estimates extra risks at various iAs doses for developing bladder cancer. Age stratified mortality and morbidity values were available for bladder cancer and were used in the lifetable analysis. At 0.13 μg/kg-day, a lifetime extra risk for bladder cancer of 7.9×10^{-4} was estimated.

d. The Toxicological Review estimates extra risks at various iAs doses for developing lung cancer. Age stratified mortality and morbidity values were available for lung cancer and were used in the lifetable analysis. At 0.13 µg/kg-day, a lifetime extra risk for lung cancer 2.4×10^{-3} was estimated.

6. Based on the lifetable analyses for lung cancer and bladder cancer, linear trend lines were used to estimate a cancer slope factor (CSF). These CSFs were estimated using only risks derived in the low-dose region given non-linearity at higher doses. Please comment on whether the selected CSF values are scientifically justified and clearly described.

7. EPA calculated a non-cancer RfD based on candidate values for each individual noncancer health outcome considered for dose-response analyses and presents the results of these analyses in Sections 4.6.

    a. EPA determined that data from the (Wasserman, 2014) study on developmental neurocognitive effects were not appropriate for candidate value derivation given the strong nonlinearity observed in the relationship between iAs exposure and IQ scores. Please comment on whether this approach is scientifically justified and clearly described.

    b. To estimate candidate values for DCS and diabetes, the meta-regression pooled slope and upper confidence limit were used to calculate a 5% response level BMD_{05} and $BMDL_{05}$, respectively. Please comment on whether this approach and the organ-specific candidate values below are scientifically justified and clearly described.

        i. For DCS, an organ-specific candidate $BMDL_{05}$ value of 0.094 µg/kg-day was derived based on increased CVD incidence.

        ii. For diabetes, an organ -specific candidate $BMDL_{05}$ value of 0.13 µg/kg-day was derived.

    c. For pregnancy outcomes, decreased birth weight was selected for benchmark dose modeling and the study-reported linear regression slope was used to estimate an organ-specific candidate $BMDL_{05}$ value of 0.23 µg/kg-day. Please comment on whether this approach is scientifically justified and clearly described.

8. EPA has evaluated and applied where appropriate uncertainty factors to account for intraspecies variability (UF_H), interspecies differences (UF_A), database limitations (UF_D), duration (UF_S), and LOAEL-to-NOAEL extrapolation (UF_L) for inorganic Arsenic.

    a. Has uncertainty been adequately accounted for in the derivation of the toxicity values? Please describe and provide suggestions, if needed

    b. For DCS, diabetes, EPA applied a $UF_H = 3$ to account for potential interindividual differences in toxicokinetics and toxicodynamics related to iAs exposure in humans. EPA determined that a higher UF_H is not necessary given that studies that investigated non-cancer effects in sensitive subpopulations were included in the meta-regressions for CVD incidence, IHD incidence, and diabetes. For all three endpoints, the study that had the largest impact on the final pooled slope value was

one that investigated effects in a sensitive subpopulation. Please comment on whether this approach is scientifically justified and clearly described.

c. For pregnancy outcomes, EPA applied a $UF_H = 3$ to account for potential interindividual differences in toxicokinetics and toxicodynamics related to iAs exposure in humans. EPA determined that a higher UF_H is not necessary as the Bangladeshi population that formed the basis of the POD for birth weight experiences low birth weight at a much greater rate than US populations and represents a sensitive subpopulation. Please comment on whether this approach is scientifically justified and clearly described.

9. From the identified human health effects of iAS and the derived organ-specific toxicity values for diabetes, DCS effects and pregnancy outcomes, an RfD of ***0.031 µg/kg-day based on increased CVD incidence in humans*** was selected. This RfD is expected to be protective against all noncancer adverse health effects associated with iAs and across all lifestages. Please comment on whether the selected RfD is scientifically justified and clearly described.