National Institute of Environmental Health Sciences (NIEHS)
Comments on the Interagency Science Consultation
Draft IRIS Toxicological Review of Inorganic Arsenic
November 2022
(Date Received December 20, 2022)

Systematic Review Methods and Documentation

NIEHS Comments: EPA's Toxicological Review (TR) of Inorganic Arsenic for the IRIS program represents an update and extension of an existing IRIS TR. As such, EPA has previously classified arsenic as carcinogenic to humans, and the current assessment considers potential updates to the quantitative estimates of cancer risk, as well as evidence synthesis of circulatory system, diabetes, pregnancy and birth outcomes, and neurodevelopmental effects. The protocol for these updates adopts systematic review methods and increases transparency and consistency over previous IRIS TRs of Inorganic Arsenic. The protocol was then released for public comment and NRC review in 2019 and subsequently updated and released October/November 2022. The adoption and incorporation of systematic review methods (included a review step) within a long-term evaluation effort is to be commended and the resulting current methods are consistent with best practices and transparent presented and followed. There are limitations to the transparency for the use of machine learning and clustering approaches to prioritize studies for evaluation of major health effects assessed in the TR. Those approaches were only applied to the initial 2012 literature search and do not present a concern or limitation to the conclusions overall.

Noncancer Hazard Identification

NIEHS Comments: The document clearly describes the available scientific evidence demonstrating that inorganic arsenic can cause cardiovascular disease (CVD); the most robust evidence is for ischemic heart disease, hypertension, and atherosclerosis. Many studies – conducted in different populations, assessing exposure by diverse methods (e.g., water levels and exposure biomarkers), and employing different study designs – found positive associations between exposure to inorganic arsenic and CVD. Suggested revisions to the draft document as detailed below would further strengthen the transparency and rationale for this assessment. Lastly, the phrase "...causes [*outcome X*] in humans given sufficient exposure conditions" is used repeatedly throughout and would benefit from some brief definition/discussion.

Tier 1

1. Strengthen the discussion across studies of key issues related to study informativeness (either in the assessment or the protocol). The report touches on some of these issues, but a more in-depth bias assessment would be helpful.
    a. Discuss the strength and limitations of the different types of exposure assessments (e.g., drinking water, urine, hair, plasma, toenail, etc.) in more detail. Discussion suggestions include how well the exposure proxy informs the exposure of interest (e.g., half-life of the biomarkers), and the direction and magnitude of any misclassification or measurement error.
        i. For example, in many studies, arsenic drinking water concentrations measured from a common drinking water source (e.g., well or other sources) are used to assign exposure at the individual level. Is this a type of Berkson error that would not bias the effect estimate (results in loss of precision), or does the overall exposure assessment also result in bias (e.g., affects the magnitude of the risk estimate)?
        ii. In cohort studies, was exposure only at baseline? If so, would that lead to exposure misclassification?

iii. The authors state (page 3-8; line 10) that total arsenic may not reflect inorganic arsenic. Is there any data on the percentage of inorganic arsenic? How were these studies rated in the study evaluation assessment?

b. Discuss whether there is a concern for exposure for reverse causation in the cross-sectional studies and case-control biomarker studies. For example, is there any reason to suspect that CVD affects kidney-related functions that might change arsenic-urinary concentrations?

c. Provide a more in-depth discussion of the identification of the main confounders (those related to both exposure and outcome and not in the causal pathway) for each specific endpoint. The protocol primarily mentions potential confounders for cancer (except for age, gender, and SES). The assessment briefly mentions some confounders for CVD but does not provide information on how they were selected. For example, BMI is stated to be a potential confounder, but it is not clear whether BMI would cause higher arsenic exposures (unless via SES) or is in the causal pathway between arsenic exposure and CVD. Do confounders differ by types of CVD? The use of directed acyclic graphs may inform the identification of confounders for studies with similar populations/designs.

d. Discuss any limitations (and direction of bias) of the SMR studies, e.g., is the general population (referent) exposed to arsenic, and thus is not an unexposed or low-exposed referent group?

e. Briefly explain why the low-confidence studies (e.g., the types, direction, and magnitude of the biases observed in these studies) were excluded. Low-confidence studies can often contribute to health hazard evaluations, e.g., by using triangulation-like methods and considering the impact of biases on study findings.

2. Strengthen the discussion of the evidence integration

a. While the discussion of the results of individual studies is adequate, the discussion of the evidence and issues across studies could be strengthen. The EPA IRIS formaldehyde report is an excellent example of how the evidence for cancer was systematically evaluated across studies by specific guidelines.

b. Provide a more in-depth discussion on whether alternative explanations such as chance, bias, and confounding can reasonably be ruled out and whether any of the biases identified decrease the confidence of the studies (e.g., the magnitude, direction, and impact of the bias on study findings).

3. Revise the forest plots and consider using tables to report the findings. The forest plots (thumbnails) are not very informative and are problematic.

a. Different types of effect estimates are plotted on the same forest plot, which distorts the visual presentation of the evidence. Some examples are

i. Figure 3-9 (Cohort and case-control studies of atherosclerosis/inorganic arsenic, OR), Wang et al. 2010 and Figure 3-10 Wang 2009. Disease prevalence (not risk estimates) is plotted for each exposure category (the points are very high).

ii. Figure 3-7 (Ecological studies SMR), Medrano et al. 2010 (2nd set of exposure categories). Percent change in disease mortality for CVD and CHD (not SMRs) are plotted.

iii. Beta coefficients (Figure 3- 13b Osorio-Yaflez 2015, Ameer 2015; Figure 3-12 a, Jiang et al. 2015) are plotted on the same graph as studies reporting ORs (e.g., positive findings appear to be null due to X-axis scale). Plot beta coefficients on separate graphs (linear scale that span from negative to positive numbers instead of a log scale from 0.1 to 100).

b. Printed figures do not have adequate information to interpret the data (e.g., study design, population, outcome measurement, covariates, type of effect estimate, units). This information may be available on the interactive plots by clicking on the study; it is needed in the printed plots in the absence of tables). Units differ between studies (e.g., some studies report mg/L and others ug/l). Figure 3-16 is labeled better than other plots.

c. Tables (per each CVD outcome) would allow the reader to see all the relevant information for each endpoint; unlike plots, the same table can report different types of effect estimates. Stratified

forest plots could be used to evaluate key issues across studies (such as exposure level, duration, type of hypertension, and population).

Tier 2

1. Page 3-42 through 3-43, Risk Modifiers. CVD varies with both Race/ethnicity and SES. Did any studies stratify the effect estimate for inorganic arsenic and CVD outcomes by these variables?
2. Appendix B. Study Evaluation: Hazard Evaluation. Beginning on page B-3, Question 3. Were the comparison groups appropriate? This question overlaps somewhat with confounding. Consider clarifying that selection bias occurs when selection into or out of the study is related to *both* exposure and disease, and when the relationship between exposure and disease is different for those who participated in the study (study population) and the source population. The same principle applies to Question 9 (beginning page B-10). Were outcome data complete without attrition or exclusion from analysis? Some systematic review methods grouped this under selection bias, e.g., selection out of the study. The additional guidance for the highest bias category briefly mentions this concept; however, it is possible to have a low bias rating when participants are lost to follow-up, but the loss is not related to exposure (non-differential).
3. Appendix B (Study Evaluation – Confounding). Residual confounding can occur if confounders are inadequately measured despite adequate statistical adjustment. It seems reasonable to integrate question 10 (confounding) and question 11 (measurement of the confounder) to determine the concern for confounding. Also, consider combining the co-exposure question with the confounding question**.**

Other comments

1. Increase the font size in forest plots and narrow the scale of the X-axis (use arrows for CI that go off the scale). Removing non-risk estimates (e.g., high numbers, see Tier 1, Question 3a) will permit a smaller X-axis scale (e.g., 100 to 10).
2. Page 3-8, lines 6 to 9. Add citations for the studies with self or proxy reports of mortality data.
3. Page 3-14, line 4. Explain why self-reported residence history and self-collected samples lead to a deficient exposure assessment. Residential history is probably reasonably recalled and not subjected to differential recall bias). Is there any data on self-collected water samples to support this judgment?
4. Figure 3-5c (page 3-13), Jin et al. 2016. It is not clear why there are two plots for each exposure category.
5. Page 3-28, Figure 3-13b. The triangles (reference group) may not be correct for these studies.
    a. Wei. The graph suggests that the triangles (inorganic arsenic) are the reference group for the specific arsenic species.
    b. Ameer and Osorio-Yanez. Plots are for the exposure (not referent) findings. See Tier 1, for comments concerning plotting beta coefficients (Ameer and Osorio-Yanez) with OR (Wei) and using appropriate scales. (Note that Ameer found a statistically significant inverse relationship with blood pressure, and Osorio-Yanez found a positive association with blood pressure, but both studies appear to be null in this graph, and oppositive directions are not apparent).
6. Pages 3-36 through 3-38. Figure 3-17 does not have all the studies mentioned in the text or plotted on the forest plots (e.g., Lewis, Farzan), and some studies mentioned in the text are not in the study evaluation ratings.
7. Page 3-36, lines 5-19. Please note the study design.
8. Appendix A (protocol). Consider replacing ‘Section 3.9 (Study/ Evaluation)’ with ‘Appendix B (Study Evaluation: Hazard Evaluation).’ Both have the OHAT questions, but Appendix C has arsenic-specific guidance (for most questions) in addition to the general questions in Section 3.9.
    a. Consider removing the text on BPA in the exposure questions in both places (Question 12, Appendix A, page C-13 through C-15 and Appendix B, Page B-16 through B-18).

b. Consider removing the text on human-controlled trials if this study design is not included in the inorganic arsenic evaluation.

9. Appendix A, Pages 3-14, line 9. Include a citation for the Report on Carcinogens.

Official Citation: NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/go/roc15 (EndNote XML)
DOI: https://doi.org/10.22427/NTP-OTHER-1003