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Comments on the External Review Draft of the IRIS Toxicological Review of Inorganic Arsenic

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Contents

1. Introduction and Overview

This document provides comments on the science considered and technical methods and approaches applied in the development of the United States Environmental Protection Agency (USEPA) Integrated Risk Information System's (IRIS) External Review Draft of the Toxicological Review of Inorganic Arsenic (Toxicological Review; USEPA 2023a) and the associated Supplemental Information (USEPA 2023b). In addition to the release of the Toxicological Review for public comment, USEPA is seeking a scientific peer review and has developed draft charge questions for this peer review (USEPA 2023c). These charge questions highlight scientific issues, as well as methods and approaches, in the Toxicological Review where USEPA is specifically requesting comments.

The comments provided in the following sections are organized based on the topics and charge questions developed by USEPA for the peer review (USEPA 2023c). While all of the charge questions were considered, a comment or response has only been provided for those charge questions where critical comments/significant points were needed. While the comments set forth in the following pages identify numerous deficiencies with the Draft Toxicological Review, a 60-day comment period for a highly technical analysis supported by voluminous (and poorly organized) documentation is not adequate. The comment period should have been extended as requested by numerous stakeholders.

Below is a brief overview of the main findings of the review. With respect to the methods used by the USEPA (2023a, 2023b):

- Reproducing USEPA's (2023a, 2023b) analyses and conclusions is difficult due to lack of clear documentation and information regarding the transparency of the methods used This assessment may not be compliant with requirements of the Data Quality Act.

- USEPA (2023a) cited the original OHAT (NTP 2013) risk of bias evaluation process as the basis for the USEPA Handbook. There have been updates to the OHAT risk of bias evaluation process (NTP 2019). The new developments in evaluating study quality and risk of bias should be applied in the USEPA (2023a, 2023b) assessment.

- USEPA's reliance solely on epidemiology evidence for drawing hazard conclusions in USEPA (2023a) is inconsistent with the IRIS Handbook, which states that evidence integration includes evidence from animal and mechanistic data (USEPA Handbook reference).

With respect to the dose-response assessment:

- It is difficult to comprehend how the agency extensively considered mechanistic evidence to inform decisions about the anticipated shape of the inorganic arsenic (iAs) dose-response relationship when only one mechanistic study related to the inherent biological dose-response relationship of iAs was cited in the Agency document (Clewell et al. 2007). In fact, this publication was an early progress report on mechanistic dose-response studies being conducted in collaboration with USEPA scientists that served as the basis for further studies, which have since been published, but were not considered in the Toxicological Review (Kenyon et al. 2008, Gentry et al. 2010, Clewell et al. 2011, Yager et al. 2013, Gentry et al. 2014a, 2014b, Efremenko et al. 2015, Clewell et al. 2018, Efremenko et al. 2021).

- USEPA (2023a) has ignored abundant mechanistic evidence supporting a MOA that indicates a threshold exists for iAs carcinogenicity, an issue which has been raised in a previous review (NRC, 2013). The previous review argued that epidemiological analyses should not be used for extrapolation below the exposure associated with increased cancer incidence in the studies. Therefore, it is remarkable USEPA (2023a; 2023b) relied solely on epidemiological data for modeling the dose-response curve.

- The Draft Toxicological Review states that "Although USEPA's modeling approach in this assessment does not assume linearity, the model slope at low doses is sufficiently linear (after visual inspection) for the derivation of a CSF". (USEPA, 2023a, p. 4-21)_There is no information presented as to whether any other methods were used to determine if the model is sufficiently linear. Figure 4-7 does not provide the citations for the source of the data points e.g., which studies provide each data point. This is a crucial deficiency in the Draft Toxicological Review.

- The use of summarized data points (e.g., figures 4-7 and 4-9) seriously calls into question the ability of the analysis to reflect the small portion of the data that is in the range of the likely threshold for the carcinogenicity of iAs (below 0.2 µg/kg-d). At the least, the model predictions should be overlaid with the actual data, rather than just the summarized values, to provide visual evidence of the appropriateness of the model assumptions. Whether the true dose-response at low exposures is distorted by the undocumented methodology or modeling approaches used by the USEPA (2023a, 2023b) cannot be determined at this time.

2. Comments on Overall Documentation

The overall documentation for the draft Toxicological Review is lacking and specifically with the documentation of the quantitative analyses. The description of the meta-regression analyses conducted are not well explained or organized in a manner that can be easily followed. The quantitative methods used lack sufficient details, resulting in a lack of transparency, that make it difficult for an expert in the field to evaluate the accuracy of the results.

For transparency, the documentation should have included all input and output files associated with the modeling, rather than in references to information external from the documentation. Multiple external references, such as Excel spreadsheets, are referred to in the draft Toxicological Review as support for the analyses conducted. Many of these external references are indicated to be available in the HERO database; however, the hyperlinks supplied in these instances take the reviewer to the main entry point for the USEPA HERO database and not to the specific reference. The HERO database for the Arsenic Hazard ID project page provides a list of more than 72,000 documents and a search for specific Excel file names (e.g. Meliker2010_CE5-27 Ln_ugperday-08-08-22.xlsx) or more general searches for .xlsx file extensions do not result in locating the files referenced in the Toxicological Review. Table 1 provides a list of information that is missing from the draft Toxicological Review (USEPA 2023a) and associated Supplemental Information (USEPA 2023b) and could not be located by searching other sources or links provided, including the HERO database. Further, there are references in USEPA (2023a) to sections in the Supplemental Information (USEPA 2023b) that do not appear to exist. Examples include references in USEPA (2023a) to:

- Appendix C.1.2.1.6 – Page 4-17, line 13 (file page 180)
- Appendix C.1.2.2.6 – Page 4-26, line 8 (file page 189) and Page 4- 43, line 33 (file page 206)
- Appendix C.1.2.2.5 – Page 4-34, line 14 (file page 197)

Without clear documentation and information regarding the transparency of the methods used in USEPA (2023a, 2023b) it is difficult to evaluate the accuracy of the analyses and conclusions in USEPA (2023a, 2023b) and this assessment may not be compliant with requirements of the Data Quality Act.

3. Comments by Topic and Charge Questions for the USEPA Peer Review

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.**

Response: Section 1.6, page 1-6 of USEPA (2023a) states "…[E]pidemiological evidence is the focus of this assessment given the abundance of epidemiological evidence and preference for using human data over animal data when available (NRC 2013); (NASEM 2019)." However, a major concern with the reliance only on epidemiological literature in the Draft Toxicological Review is that there is no effort to assess the adequacy of the epidemiological evidence for characterizing the dose-response in a way that is consistent with the mode of action (MOA) for the toxicity and carcinogenicity of iAs. This is important for multiple endpoints considered by USEPA (2023a); however, this deficiency is particularly important in the case of cancer endpoints, where a nonlinear mode of action has been delineated based on the results of several studies that were not considered in the Toxicological Review, including:

Gentry et al. 2010
Clewell et al. 2011
Yager et al. 2013
Gentry et al. 2014a, 2014b,
Clewell et al. 2018,
Efremenko et al. 2015, 2021

Further, USEPA (2023a) states… "With respect to the animal data, most adult laboratory animal models appear to be less susceptible to inorganic arsenic than humans when comparative information is available (Lynch et al. 2017a); (Lynch et al. 2017b); (Vahter 1994); (Vahter and Norin 1980)." If epidemiological evidence remains the only focus of this assessment, performing an adequate integration of animal, epidemiological and mechanistic information to support a scientifically plausible dose-response assessment will be impossible. One example of an integration of animal, epidemiological and mechanistic information is provided in Tsuji et al (2019), an analysis performed for the Texas Commission on Environmental Quality (TCEQ) as a follow-on to the Lynch et al. (2017a, 2017b) study, which, similar to the Agency's analysis of inorganic arsenic (USPA 2023a), did not incorporate the available mechanistic MOA evidence into their epidemiological meta-analysis.

Based on USEPA's guidance for developing IRIS assessments (USEPA 2022), "evidence integration combines animal and human evidence synthesis judgments while also considering information on the human relevance of findings in animal evidence, coherence across evidence streams ("cross-stream coherence"), information on susceptible populations or lifestages, understanding of biological plausibility and MOA, and potentially other critical inferences (e.g., read-across analyses) that can draw on mechanistic and other supplemental evidence." Therefore, USEPA's reliance only on epidemiology evidence in USEPA (2023a) and using animal and mechanistic evidence as potential supplemental material, is inconsistent with the IRIS Handbook. NRC (2014) has explicitly stated that evidence integration is typically performed considering human, animal, and mechanistic evidence. Consideration of only epidemiological studies may also eliminate

studies that may be critical in characterizing the shape of the dose-response curve at low concentrations, considering that epidemiological studies of low exposure concentrations frequently show risks that are not distinguishable from null for a variety of reasons (for example, differences in inter-individual variability in diseases or related to physiological processes that affect internal doses).

Multiple literature searches have been conducted for the Toxicological Review over the span of a decade. The search strategies for these literature searches do not appear to be well documented or updated for each iteration of the Toxicological Review, making it very difficult to understand why certain studies were not included or considered. USEPA states that literature searches and updates were completed between 2012 and 2019; and following prioritization of the six select outcomes, another literature search was conducted in 2022.

According to the PECO criteria (Table 1-2, p. 1-7), "Health outcomes of interest, based on hazard judgment, relative risk over the background exposure (RRB), and potential use for benefit-costs analysis by program offices, include bladder cancer, lung cancer, diseases of the circulatory system (DCS), diabetes, pregnancy and birth outcomes, and neurodevelopmental effects". USEPA (2023a) states that following the prioritization of the six select outcomes, an additional literature search was conducted in 2022. It is unclear if the literature search keywords that were applied in 2013, 2016, and 2019 were also used for the 2022 updated search or if new or limited keywords focusing only on the six selected outcomes were used in 2022. Articles focusing on other outcomes of potential interest could have been missed if the most recent searches were only targeting the six outcomes of interest.

Literature search strategies were provided in the USEPA 2019 iAs protocol update (Appendix B, Table B-1) and USEPA 2023 iAs protocol update (Appendix B, Table B-1) and in both tables, it states searches were conducted in January and December of 2013 and in December of 2016. If additional searches were conducted for the subsequent updates of the Toxicological Review in the years 2019 and 2022, these dates should have been updated in the tables. The reader should not have to go back to previous drafts of the Toxicological Review to see the literature search strategies and key words. A complete history of the literature search strategy and keywords used for each iteration of the literature searches should be presented transparently in the most recent draft of the assessment.

In section 1.6.1 on page 1-8, USEPA (2023a) indicated several types of studies that did not meet the PECO criteria could have potentially contained relevant supplemental materials and could become critically important to the assessment. USEPA (2023a) notes that these materials, which may include epidemiological studies on health outcomes other than those listed in the PECO statement, animal toxicity studies, meta-analyses, studies that do not meet PECO inclusion criteria but include health effects relevant to the PECO, kinetic studies, and exposure assessments may need to be evaluated and summarized at the individual study level. If these types of studies are identified and considered supplemental and critical, the PECO statement should be updated, and additional literature searches should be conducted to identify any similar data that may not have been identified during the initial literature search.

It should also be noted that the references to "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)" in the charge questions (USPEA 2023c) are incorrect. The correct Section is 1.6.1 for Literature Searching and Screening and Appendix B for the Updated Problem Formulation and Protocol for Inorganic Arsenic IRIS Assessment.

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.

Response: According to Section 1.6.2 on page 1-9, the risk of bias for each study was evaluated across seven domains using a tool adapted from the OHAT approach proposed in 2013 (NTP 2013) with arsenic-specific clarification as needed. However, the OHAT approach proposed in 2013 has been updated since the original arsenic protocol was completed. Additionally, USEPA's IRIS and TSCA programs have developed protocols for determining risk of bias and data quality. Therefore, over a decade of consideration and updates to the original OHAT (2013) risk of bias evaluation process has been applied and new approaches in evaluating study quality and risk of bias have been developed and should be applied in the USEPA (2023a, 2023b) assessment.

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.

Response: It is unclear if data extraction was performed on the data identified in the most recent literature searches conducted in 2022. In Section 1.6.3, USEPA (2023a) indicates data extraction and content management was initially carried out using ICF's DRAGON and Litstream before subsequent migration to HAWC in 2021. USEPA (2023a) also notes studies concluded to be uninformative were not considered further and did not undergo data extraction. Figure 2.2 of USEPA (2023a) indicates 169 studies from the most recent search conducted in 2022 were considered relevant following full text screening. However, a search of the study quality and risk of bias spreadsheets accessed through a link provided in the Toxicological Review (USEPA 2023a) indicated no studies published from 2019 to 2022 were considered for quality assessment. It appears that none of the 169 studies identified in 2022 were considered "informative" and included in data extraction and there was not adequate time during the 60 day timeframe for comments to fully review and conduct risk of bias evaluations to verify the relevancy of these studies.

Noncancer Hazard Identification

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.

Response: The presentation of the data in the Draft Toxicological Review makes it difficult to assess whether the "evidence demonstrates" or "evidence indicates" hazard assessments are scientifically justifiable.

- *The forest plot visualizations are difficult to interpret easily because the exposure comparisons (e.g., cumulative arsenic in drinking water, average arsenic drinking water) and units (e.g., ppb, ppb-years, µg/L, µg/L years, µg/L/kg-day) differ widely (or are not necessarily identified in the forest plots). All exposure comparisons from a single study are grouped together on a forest plot. A more helpful approach would be to group the comparisons for the same exposure metric on the same forest plot (for example, group the results that used cumulative exposure on a plot for comparisons and group the risks for the different studies that used average daily exposure on a plot). It would be helpful to have more figures with comparable exposure units (e.g., all cumulative exposure results from different studies in one visualization, with ppb-years converted appropriately to ug/L-years, and average concentrations (with ppb converted to µg/L) in another visualization).*

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).

Response: In the hazard assessment for DCS, it would be helpful to lay out the proposed biological pathway by which inorganic arsenic exposure causes cardiovascular effects in humans. Presumably, the development of atherosclerosis and hypertension precede the increased incidence (or mortality) of ischemic heart disease. The development of hypertension may also increase the incidence or mortality of stroke. Prolonged QT interval suggests electrolyte disturbances. Perhaps there is a relationship with atrial fibrillation, or other electrical disturbances of the heart. Factors affecting electrical disturbances may differ from factors affecting the development of atherosclerosis. A clearer evaluation of the mechanistic data and the pathway from iAs exposure to clinical effects and population-level effects could support (or be used to argue against) the evidence synthesis.

Figure 3-3 of USEPA (2023a) states that 171 studies of DCS were identified: 84 were determined to be of medium or high confidence, 29 were of low confidence or uninformative, and 48 were identified post-2019. For these latter 48 studies, the USEPA did not consider them as part of the hazard assessment for DCS because the hazard was established. Did the USEPA rely solely on the NRC (2013) report for the establishment of the hazard, i.e., "evidence demonstrates"? If it did, why did it include a full review of epidemiological studies until 2019? On the other hand, if the USEPA reviewed all studies until 2019 and concluded that the "evidence demonstrates", that evidence is being peer-reviewed for the first time with this draft Toxicological Review. If the latter is the case, it is not clear why the post-2019 studies were not considered as part of the hazard assessment. Also, the USEPA (2023a) states that none of the 48 studies post-2019 were relevant for meta-regression. The 48 studies identified post-2019 represent 28% of the 171 studies, a large proportion. Did none of the post-2019 studies have information that pertained to low exposure? There may still be relevant qualitative information in these studies even if none of them were relevant for meta-regression analysis. Some examples of the 48 studies that were

excluded and may be relevant (based on a review of abstracts include): cardiovascular disease mortality (Xu et al. 2020; Kuo et al. 2022; Al-Forkan et al. 2021; Nigra et al. 2021; among others) and hypertension (Desai et al. 2021; Liu et al. 2022; Rahmann et al. 2022; Kaufman et al. 2021).

There were 27 studies of incidence of or mortality from CVD/IHD, all of which received an overall confidence rating of "probably low risk of bias" or "definitely low risk of bias" (Figure 3-4 Study evaluation ratings for references, p. 3-8). Two of the most critical elements in the risk of bias domains are related to the exposure characterization and confounding. Of these 27 studies, 12 studies were rated as having probably high risk of bias related to confounding. Separately, 13 studies were rated as having probably high risk of bias related to exposure characterization. There was no information in HAWC to justify the overall ratings of "probably low risk of bias." Importantly, what are the most potential sources of bias in these studies? USEPA (2023a) should provide the most important sources of bias in the text. Which confounders were considered, and which confounders were adjusted for in the analyses? Which studies are low-exposure studies and which studies are high-exposure studies?

The NRC (2013) report described the "key considerations for the IRIS assessment" for cardiovascular disease (but not necessarily all DCS):

> *In evaluating the causal relationship between arsenic exposure and cardiovascular diseases, however, USEPA should address potential uncertainties resulting from differences between the study population and the general population. Animal data and data that reveal potential modes of action demonstrate sensitivity of the cardiovascular system to arsenic exposures relevant to humans and support identification of modes of action. That can be useful for supporting causality in the epidemiologic studies, help to identify sensitive populations, and inform the dose–response analysis. (NRC 2013, p. 31)*

Below are some issues related to the evidence judgment ("evidence demonstrates") that iAs causes DCS (p. 3-46, Table 3-2, p.3-48):

The key finding for cardiovascular disease/IHD incidence and mortality, reported in the evidence profile table (Table 3-2), relates to low exposure studies:

> *Large, prospective cohort studies support exposure-dependent associations of relatively low exposures to iAs in drinking water (<100 µg/L). (USEPA 2023a, p. 3-48).*

It would be helpful to cite the large prospective cohort studies in the table. These studies cannot be easily determined based on the information presented in the forest plots and study evaluation ratings (risk of bias summary figures). Case-control studies and cohort studies are described in the narrative together under a heading "case-control and cohort studies" (p. 3-9).

Regarding the factors included in Table 3-2 of USEPA (2023a) that increase or decrease certainty, these factors do not appear to address this key finding specifically.

- *The USEPA states "most studies are medium or high confidence" as a factor that increases the certainty of the key finding. Is this referring to the "large prospective studies" in the key finding? Or is it referring to the entire body of human studies? The USEPA also reported "Consistency – across study types, including cross-sectional, and ecological "natural experiments;" across populations including U.S., Bangladesh, China, Taiwan, and Mexico" increases certainty in the key finding. The results are not presented according to study type in the forest plots. The forest plots should group the studies by study design. In addition, "Consistency" in the direction or magnitude of the overall risk estimates cannot easily be evaluated because it is not easy to identify which studies (and how many) are cross-sectional studies, which studies (and how many) are cohort studies,*

which studies (and how many) are case-control studies, and which studies are natural experiments. The results of all studies are presented in forest plots.

The USEPA stated that a "Large or concerning magnitude of effect – large odds ratios in some studies" increased the certainty.

- *Which studies reported large odds ratios? What is the magnitude of a "large" odds ratio? Are the odds ratios of similar magnitude to other estimates of relative risk? Odds ratios may be overestimated when the disease is not a rare disease.*

The USEPA reported that "Dose-response gradient – observed in many studies" increased the certainty of the evidence in the key finding. Again, is this related specifically to the key finding, i.e., "large prospective cohort studies" and "relatively low exposures to iAs in drinking water."?

- *Which studies identified a dose-response gradient and at what concentrations? The forest plots include studies of different measurement units (e.g., ppb, µg/mL) and different exposure metrics (cumulative exposure, average exposure). This makes the results difficult to compare. Which studies did not identify a dose-response gradient and what were the differences between the studies that did and the studies that did not? (For example, did certain studies adjust for different confounders)? The ORD Handbook suggests grouping studies by study design.*
- *There are two issues related to dose-response gradients for the noncancer hazard identification: 1) the biological gradient should be considered as one of modified Hill considerations for the hazard identification (as a factor that increases the certainty of the evidence), and 2) can the existing epidemiological data be used for dose-response for purposes of the risk assessment? It is reasonable that the biologic gradient can be demonstrated in the hazard identification (issue 1); however, there must still be an assessment of whether the existing epidemiological data can be used for purposes of the dose-response assessment. USEPA (2023a) claims the epidemiological can be used for dose-response and uses a meta-regression for a dose-response meta-analysis. The limitations of this are discussed in the charge questions related to the meta-regression.*

With respect to "Coherence with findings for related endpoints" as a factor that increases the certainty:

- *Hypertension is discussed as its own endpoint in the same table (Table 3-2 of USEPA, 2023a). The evidence synthesis judgment for hypertension was described as "robust"; however, robust evidence does not seem consistent with the key finding for hypertension:*

  "Some, but not all, well-designed cohort studies report positive associations. Results are sensitive to the choice of exposure metric."

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).

Response: Similar to the issues raised for CVD/IHD, when did the USEPA judge that the "evidence demonstrates" a causal relationship? Studies published after 2019 were not considered because the USEPA stated that the hazard judgment ("evidence demonstrates") had been established. Furthermore, the new literature would not inform the hazard judgment (see USEPA Figures 3-3, 3-21). The NRC (2013) report provided a recommendation to prioritize diabetes as an endpoint to assess but did not itself conclude that diabetes was causally associated with iAs. Of the 112 epidemiological studies of diabetes, 41 were identified post-2019 and USEPA (2023a) indicated that for these studies "hazard established and not suitable for meta-regression" (Figure 3-21, p. 3-51). In other words, USEPA (2023a) claims that more than one-third of the studies

were not considered for the hazard assessment and did not have useful data for the meta-regression. Even if these studies did not have quantitative dose-response data, these studies may still have important information that informs the dose-response and the overall evidence regarding low exposures. Do any of these studies provide data that conclude that the risk of diabetes was not increased at low exposure concentrations even if the quantitative data were not suitable for meta-regression?

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.***

Response: For pregnancy and birth outcomes, the post-2019 studies were excluded based on "lack of hazard and/or dose-response utility", although USEPA (2023a) reported that these studies underwent assessment for risk of bias. This "lack of hazard and/or dose-response utility" statement is confusing, and it is unclear how these studies contributed to the evidence. Of the 102 studies of pregnancy and birth outcomes, 68 were described as medium or high confidence studies, 22 as low confidence or uninformative, and 12 were identified as post-2019 and tagged as having "lack of hazard and/or dose-response utility" (Figure 3-26, p. 3-68).

Of the 13 studies that evaluated fetal and infant mortality (Figure 3-27), all were given an overall confidence rating of probably low risk of bias and/or definitely low risk of bias. The different domains assessed should not be weighted equally. Of particular importance are those domains related to exposure characterization and confounding. In this example (Figure 3-27), 7 studies were rated "probably high risk of bias" for exposure characterization; 2 studies were rated "probably high risk of bias" for confounding or effect modification that was not accounted for in the design or analysis; and 5 studies were rated "probably high risk of bias" for confounding that was not assessed consistently across groups using reliable measures. Separately, the study by Myers et al. (2010) was identified as having a "probably high risk of bias" for six domains (comparison group, confounding, adjusting for other exposures, consistent assessment of confounding, exposure characterization, and outcome characterization) of the total 11 domains. The overall justification for a confidence rating of "probably low risk of bias" should be justified for these studies. There is no additional information in HAWC that justifies the overall confidence ratings. It would be helpful to identify the most important sources of bias for the body of literature and describe how the studies addressed them.

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.

Response: For neurodevelopmental effects, the post-2019 studies were excluded based on "lack of hazard and/or dose-response utility", although the USEPA reported that these studies underwent assessment for risk of bias. This "lack of hazard and/or dose-response utility" statement is confusing. Figure 3-28 describes 72 studies of neurodevelopmental effects (primarily cognitive effects) of which 52 were studies of medium or high confidence, 17 were of low confidence or uninformative, and 3 were identified post-2019. Justification for the overall confidence ratings were not provided in HAWC. Ratings of "probably high risk of bias" for some of these domains are more important than other domains and the likely impacts should be addressed in the overall confidence rating.

Meta-Regression Analysis

4. **USEPA performed 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.**

Response: The USEPA uses Bayesian meta-regression to conduct a dose-response analysis of the epidemiological data for both cancer and noncancer endpoints, so this response provides general comments on the overall approach, using specifics for individual endpoints where needed. Bayesian meta-regression is a powerful approach for analyzing multiple studies, but it is highly susceptible to unintended bias associated with the selection of dose-response models and the definition of quasi-informative prior distributions for model parameters.

The dose-response model used in the meta-regression for lung and kidney cancer is a multiplicative exponential model that is mathematically incapable of describing the threshold dose-response expected for iAs carcinogenicity from the MOA evidence and would tend to force the relationship at low doses to appear linear. Therefore, the meta-regression method (including the selection of the exponential model) is not scientifically justified.

In addition, due to the unavoidable impact of exposure error in the studies, the observed dose-response can differ significantly from the true dose response, with a tendency toward linearization of the apparent dose-response (Crump 2005, Rhomberg et al. 2011).

The Bayesian meta-regression analysis by Shao et al. (2021), which is criticized in the draft Toxicological Review, considered the use of a logistic model similar to USEPA's, but determined that it was inappropriate for use in the case of iAs due to its incompatibility with the threshold dose-response expected based on the MOA for iAs carcinogenicity. USEPA's use of a logistic model calls into question the biological plausibility of their dose-response predictions in the low-dose region that is more relevant to human exposures. The key advantage of the Hill model is that it avoids loss of information in the low-dose region due to the influence of the preponderance of data at higher concentrations.

The dose-response modeling for individual outcomes in USEPA (2023a, 2023b) is limited to meta-regression analyses and is conducted using data solely from epidemiological studies, and there is no effort to assess the adequacy of the epidemiological evidence for characterizing the dose-response in a way that is consistent with the mode of action (MOA) for the toxicity and carcinogenicity of iAs. This deficiency is particularly important in the case of cancer endpoints, where a nonlinear mode of action has been delineated based on the results of several studies noted previously (Gentry et al. 2010, Clewell et al. 2011, Yager et al. 2013, Gentry et al. 2014a, 2014b, Clewell et al. 2018, Efremenko et al. 2021). Therefore, the only valid approach for determining the low-dose behavior of the carcinogenic effects of iAs observed in epidemiological studies is the consideration of dose-response data from in vitro studies with human cells.

The lack of consideration of these data in the dose-response modeling is all the more remarkable because the challenge that the agency has faced in previous risk assessments for iAs was concern that the agency was ignoring the abundant mechanistic evidence indicating that because of the threshold nature of the MOA for iAs carcinogenicity, epidemiological analyses could not be used for extrapolation below the exposures associated with increased cancer incidence in the studies. As the available mechanistic studies demonstrate, the mode of action for the carcinogenicity of iAs involves disruption of cellular signaling by the ability of iAs and its metabolites to bind avidly to vicinal dithiols in key cellular signaling proteins, leading to disruption of inflammatory and oxidative stress signaling and, at sufficiently high concentrations (above 20-50 ppb in drinking water), inhibition of the cell's DNA damage response. This inhibition of DNA damage repair, overlaid on a background of co-exposure to mutagenic chemicals or radiation in the environment, underlies the observed co-carcinogenicity of iAs in the skin, lung and bladder.

This failure of USEPA (2023a, 2023b) to consider MOA data may relate to the fact that in the iAs IRIS Protocol USEPA conducted a case study using idiopathic bladder cancer and concluded that MOA analyses were not more suitable than the epidemiological studies for reaching conclusions about the shape of the dose-response curve in the low-dose region. This is a remarkable finding, given that for many years there has been strong evidence from mechanistic studies that the dose-response for the carcinogenicity is highly nonlinear (Snow et al. 2005, Kitchin and Wallace, 2008), with a threshold for carcinogenicity from drinking water exposures on the order of 20-50 ppb (Gentry et al. 2014b, Tsuji et al. 2019). On the other hand, this conclusion by the agency is unfortunately consistent with their previous risk assessments for chemicals with a nonlinear cancer MOA, including formaldehyde and dioxin, in which they have ignored or disputed MOA evidence in order to support their preference for a linear, no threshold low-dose extrapolation (Clewell et al. 2019), despite NAS recommendations to apply dose-response approaches more consistent with the evidence for a nonlinear MOA for these chemicals.

The focus on probabilistic analyses of epidemiological data ignores the crucial MOA evidence from mechanistic studies that the effects of inorganic arsenic result from chemical interactions with thiols in key cellular signaling proteins, disrupting control of oxidative stress, inflammation, DNA repair and replication, not from mutagenicity (Snow et al. 2005, Kitchin and Wallace, 2008, Clewell et al. 2018, Tsuji et al. 2019, Efremenko et al. 2021). Therefore, data in the range of observation of increased incidence (above 20 ppb in drinking water) is not informative for the dose-response at lower exposures.

The Agency states (Toxicological Review, p. 1-6) that "Mechanistic evidence has also been extensively considered during the course of preparing this assessment, especially in the context of addressing differences in anticipated response among humans (e.g., between children and adults) and to inform decisions about the anticipated shape of the dose-response relationship. Ultimately, the epidemiological evidence was comprehensive and sufficient to inform these judgments." However, it is difficult to comprehend how the agency extensively considered mechanistic evidence to inform decisions about the anticipated shape of the iAs dose-response

relationship when only one mechanistic study related to the inherent biological dose-response relationship of iAs was cited in the Agency document (Clewell et al. 2007). In fact, this publication was an early progress report on mechanistic dose-response studies being conducted in collaboration with USEPA scientists that served as the basis for further studies, which have since been published, but were not considered in the Toxicological Review (Kenyon et al. 2008, Gentry et al. 2010, Clewell et al. 2011, Yager et al. 2013, Gentry et al. 2014a, 2014b, Efremenko et al. 2015, Clewell et al. 2018, Efremenko et al. 2021).

The conclusions reached regarding low-dose behavior can be very dependent upon the epidemiological studies used to evaluate the dose-response in the low concentration region. Several epidemiological studies that have measured arsenic concentrations in drinking water at low concentrations and evaluated cancer endpoints are not included in the current draft Toxicological Review as part of the meta regression analyses (Guo et al. 1997; Chiou et al. 2001; Lewis et al. 1999; Karagas et al. 2004; Lamm et al. 2004; Han et al. 2009; Baastrup et al. 2008).

IRIS draft report page 4-21 (physical page 164) text states that "Although USEPA's modeling approach in this assessment does not assume linearity, the model slope at low doses is sufficiently linear (after visual inspection) for the derivation of a CSF". Was any other method used to determine if the model is sufficiently linear? Figure 4-7 does not provide the source of the data points e.g. (which studies provide each data point). This is a crucial deficiency in the draft Toxicological Review. The extensive summarization of data indicated by the symbols in Figures 4-7 and 4-9 seriously calls into question the ability of the analysis to reflect the small portion of the data that is in the range of the likely threshold for the carcinogenicity of iAs (below 0.2 µg/kg-d). At the least, the model predictions should be overlaid with the actual data, rather than just the summarized values, to provide visual evidence of the appropriateness of the model assumptions.

The use of summarized data-points in these figures reflects the opacity of the entire document. It is simply not possible for an expert in the field to determine the extent to which the methodology used by the USEPA (2023a, 2023b), which is essentially undocumented at this time, could distort the true dose-response at low exposures.

General issues with meta-regressions should be discussed in USEPA (2023a, 2023b) (Rothman et al. 2008; Greenland 1987; Greenland and Longnecker 1992): e.g., aggregation bias, meaning associations between average (grouped) subject characteristics and the pooled exposure effect may not reflect a true association between individual subject-level characteristics and the exposure effect. There are also issues when the number of studies is small, as with diabetes (four studies) and ischemic heart disease and cardiovascular disease incidence. Furthermore, the studies of diabetes appeared to group type 1 and type 2 diabetes, which is another example of aggregation bias. Type 1 and type 2 diabetes are likely to have different (and distinct) biological pathways to disease and anticipated modes of action. Type 1 diabetes is mediated via autoimmune responses that destroy β cells and insulin producing cells in the pancreas (potentially triggered by a virus). Although Type 2 diabetes is also characterized by β cell apoptosis, cell death occurs due to glucose intolerance, insulin resistance and reduced insulin secretion (Paschou et al. 2018; Giwa et al. 2020; Galicia-Garcia et al. 2020; Cnop et al. 2005).

In general, there is an inadequate description of tests of the underlying assumptions regarding the analyses and whether any assumptions were violated and what the implications are for the results if assumptions do not hold. There are many references to Allen et al. (2020a, 2020b) for further description of the methods; however, the methods should be specifically stated in the documentation. This lack of adequate description of methods in USEPA (2023a, 2023b) results in it being unclear exactly how the meta-regression analyses were performed. The input and output files for the Stan modeling should be provided so this information could be ascertained. In addition, on page C-98 (file page 154) it states that an alternative Bayesian meta-regression was

performed and is available in the references available from the USEPA HERO database; however, as with other external references, no files are provided, so this information is not available.

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, and hierarchical Bayesian methods to estimate pooled slopes of the relationship between extra risk and dose, are scientifically justified and clearly described.**

Response: Equations provided in Appendix C to explain the process of producing effective counts are incomplete leaving it up to the reader to derive the necessary equations from the given equations to check the process. Although again it is stated in the text that spreadsheets are provided that automate the process (USEPA 2023a, 2023b), no direct links to spreadsheets are given in the document, no spreadsheets were provided within the docket, and the links provided in the document takes the reader to the general page for USEPA HERO database. A search of the HERO database did not identify any excel spreadsheets or files with the names provided in the Draft Toxicological Review. It should be more evident how effective counts were calculated (e.g., more straightforward presentation of relevant equations, sample calculations, etc.) and the justification provided for how those effective counts account for potential confounders (e.g., weight) affecting one group over the other.

The method used in the meta-regression analysis to calculate effective counts constrains the confidence intervals so that they match the reported adjusted results. This is a different approach than Greenland and Longnecker (1992), which is cited in the draft Toxicological Review. The rationale provided by Allen et al. (2020a) is: "to preserve the original group characteristics to the extent possible – adjusting counts to derive effective data that might have been collected had the covariate levels remained the same as in the referent group." However, this ignores potential issues with the referent group that can arise in categorical analysis of case-control studies. Rothman et al. (2008) states "The dependency of relative risks on background (unexposed) risks cannot be examined among case-control studies, because the latter usually do not provide information on background risks." Because this is a novel approach to deriving a "common" dose-response, it would be helpful to see differences between effective count adjustments using Greenland and Longnecker (1992) as well as making a comparison to conventional dose-response assessment (i.e., evaluating dose-response from the highest quality studies by identifying a POD and noting the limitations. If there are striking differences between "high exposure" and "low exposure" studies, this also suggests a nonlinear mode of action that supports a more biologically-based (and not statistically-based) dose-response.

The combination or pooling of slope factors, as described in footnote c to table ES-1 of USEPA (2023a), are conducted using a method that assumes that a normal distribution defines the relationship between Benchmark Doses (BMDs) and the lower bound on the Benchmark Doses (BMDLx). The documentation does state that this is conducted on an assumption of normality; however, but no justification or additional information about validity of that assumption is given or the impact of this assumption of the results. This should be provided. Some additional questions around the meta-regression analyses include:

- *What is the justification for transforming published iAs exposure categories into a continuous measure, particularly when there is a significant discrepancy in statistically significant outcomes between various studies? (For example, most studies for bladder cancer in Table C-19 indicate lack of statistical significance (i.e., RR/OR 95% CI includes 1) until higher exposure categories, so derivation of such small outcome values requires explicit statement of assumptions. Are hierarchal or non-hierarchal plots used for filling in RR/OR values in Table C-20?*

- *Are there any other model types that could have been tested?*
- *Please do a better job documenting dose conversions. There are referenced sections that don't exist (Section 5.3 in Appendix A), and all of the factors/variables underlying the dose conversion should be available for each study. The calculation of extra risk is dependent upon the lifetable analysis; however, the lifetables referenced appear to be missing.*

7. USEPA 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. 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 BMDL05 value of 0.21 µg/kg-day. Please comment on whether this approach is scientifically justified and clearly described.

Page ES-4: Footnote b in Table ES-2 states that the US median dietary background dose used in estimating the $BMDL_{05}$ is 0.02 µg/kg-day – but the calculation reported in footnote b does not match the 0.210 estimate reported. If calculated from the $BMDL_{05}$ from the RfD, using the UFc, it appears the $BMDL_{05}$ reported should be 0.23 (rounded from 17.3 * 0.012 + 0.02 = 0.2276) as that is the only dose which would give the reported RfD in Table ES-2 for pregnant women of 0.077 (e.g., 0.23/3 = 0.766).

Table 1. References to Excel files or Spreadsheets not provided in documentation or with link to only HERO Database not specific files

Location of reference	Page	Description	Filename
Draft Toxicological Review (USEPA 2023a)	184 – page 4-21	meta-regression models and lifetable spreadsheets	Not provided
	190 – page 4-27	meta-regression models and lifetable spreadsheets	Not provided
	205 – Page 4-42	meta-regression models and lifetable spreadsheets	Not provided
	212 – Page 4-50, footnote in table 4-12	Meta-regression models and lifetable spreadsheets used to derive the values in the table	Not provided
Supplemental Files (USEPA 2023b)	59 – Page C-3	A simple likelihood maximization routine, implemented with an Excel spreadsheet (see Supplemental Material) is missing.	Not provided
	63 – page C-7	see "LOGNORMAL" vs. "ORIGINAL" results, Main tab, Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx , Supplemental Material, bladder cancer intake uncertainty folder, EPA 29 HERO database)	Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx
	64 – Page C-8	conversion factor validation spreadsheet available from a link within the EPA inorganic arsenic HERO project database	Not provided
	64 - page C-8	"LOGNORMAL" vs. "ORIGINAL" results, Main tab, Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx , Supplemental Material, bladder cancer intake uncertainty folder, EPA HERO database	Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx
	67 – page C-11	"LOGNORMAL" vs. "ORIGINAL" results, Main tab, Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx , Supplemental Material, bladder cancer intake uncertainty folder, EPA HERO database	Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx
	67 - page C-11	see "LOGNORMAL" vs. "ORIGINAL" results, Main tab, Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx , Supplemental Material, bladder cancer intake uncertainty folder, EPA 29 HERO database)	Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx
	73 – page C-17	automated in a spreadsheet provided in the Supplemental Material	Not provided
	77 – page C-21	The adjustments of counts for both case-control and cohort studies, and of expected values for incidence rate cohort studies, have been automated in an Excel spreadsheet (see Supplementary Material).	Not provided
	83 – page C-27	Spreadsheets that were developed to implement the approach are provided in Excel files that are included in the supplemental Material available from the EPA HERO database	Not provided

Table 1. References to Excel files or Spreadsheets not provided in documentation or with link to only HERO Database not specific files			
Location of reference	**Page**	**Description**	**Filename**
	113 - page C-57 footnote of Table C-18	Conversion Factor Validation spreadsheet for justifications for individual exposure factors	Not provided
	139 - page C-83 footnote of Table C-28	Conversion Factor Validation spreadsheet for justifications for individual exposure factors	Not provided
	160 – page C-104 in footnote of Table C-30	Conversion Factor Validation spreadsheet for justifications for individual exposure factors	Not provided
	177 – page C-121 in footnote for Table C-44	Conversion Factor Validation spreadsheet for justifications for individual exposure factors	Not provided

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