Charge to the National Academy of Sciences (NAS) Ad Hoc Committee for the Evaluation of the Protocol for the IRIS Toxicological Review of Inorganic Arsenic

May 2019

The U.S. Environmental Protection Agency (EPA) requests that the NAS perform a review of the inorganic arsenic problem formulation and protocol documents to evaluate the revised scope of the assessment, and whether the methods outlined in the protocol are appropriate to synthesize the scientific evidence and quantitate estimates of toxicity. The committee will evaluate EPA's protocol and associated documents using the charge questions set forth below. The committee will not conduct an independent assessment of the potential human health effects of inorganic arsenic.

Since January 2017, EPA's Integrated Risk Information System (IRIS) Program has been working to modernize its workflow. As part of this modernization, IRIS has moved away from one-size-fits-all assessments to a portfolio of chemical evaluation products to meet specific decision contexts. This approach optimizes the pragmatic application of best practices in systematic review in the IRIS Program, including, where possible, for assessments that were ongoing. In December 2018, EPA reaffirmed inorganic arsenic as a priority IRIS assessment for Fiscal Year 2019 (see https://www.epa.gov/iris/iris-program-outlook), and as such, IRIS is proceeding with development of this assessment to meet the current needs of the Agency.

EPA has developed an updated problem formulation and protocol document that presents adjustments to the 2015 draft Assessment Plan (U.S. EPA, 2015). It specifies which health outcomes are being prioritized for dose-response analysis and toxicity value derivation, the type of evidence considered most informative for the assessment, and the systematic review, dose-response, and other methods proposed for use in developing the assessment. The refined scope presented here was informed by prior science discussions with the National Research Council (NRC), EPA program and regional offices, and other stakeholders. Past NRC conclusions and recommendations included:

- The committee concluded that human data are expected to be the basis for dose-response analyses but should the epidemiological data in the range of observation be inadequate to meet EPA's needs, mode-of action (MOA) data should be used to the extent possible to extrapolate below the observed range (NRC, 2013).
- The committee suggested that health outcomes included in the assessment should be tiered and further prioritized given the volume of data on inorganic arsenic, particularly human data (NRC, 2013). The NRC provided recommendations on three tiers of outcomes, specifically Tier 1 (evidence of a causal association determined by other agencies and/or in published reviews), Tier 2 (other priority outcomes), and Tier 3 (other endpoints to consider). NRC also advised EPA to further refine these categorizations after conducting a more comprehensive analysis.
- The committee supported EPA's proposal to consider animal and mechanistic data as supporting evidence for determining causality (NRC, 2013).
- The committee agreed with EPA's proposal to conduct dose-response analysis for *causal* or *likely causal* relationships, even in the absence of understanding the potential mode-of-action(s) (MOAs) (NRC, 2013).
- The committee supported EPA's plan to conduct MOA analyses to determine whether the available MOA evidence is expected to be useful for informing the dose-response of health outcomes classified as having a *causal* or *likely causal* relationship with arsenic (NRC, 2013).

- The committee supported EPA's dose-response meta-analysis approach for epidemiological studies (NRC, 2013).
- The committee agreed with use of the PBPK model by El-Masri et al. (2008) to understand the relationship between drinking water and urinary concentrations of arsenic, as presented to the NRC in 2015 (https://www.epa.gov/iris/inorganic-arsenic-meetings-webinars).

Charge questions on the Updated Problem Formulation and Protocol

1. The Agency utilized systematic review (§ 3, Appendices B and C) and NRC's prioritization tiering (NRC, 2013) to assist in prioritizing health outcomes for dose-response analysis and toxicity value derivation. Please comment on this approach for prioritizing health outcomes.
2. Please comment on the clarity and appropriateness of the systematic review methods described (§ 3, Appendices B, C, and D), including: the Populations, Exposures, Comparators, and Outcomes (PECO) criteria; literature search and screening, study evaluation, and data extraction procedures; and the approach for evidence synthesis.
    a. The EPA has considered a wide range of human health outcomes, including pregnancy outcomes and developmental neurotoxicity, in the hazard identification and dose-response analyses in the assessment. Please comment on whether this approach adequately addresses potential health effects from early life exposures?
3. The NRC (2013) recommended that, if feasible, EPA conduct MOA analyses to improve understanding of low-dose exposure-response relationships. During the course of the arsenic assessment EPA has conducted inventories of mechanistic evidence and an extensive MOA analysis on bladder cancer to inform the feasibility and utility of such efforts. Based on these efforts (§2.3.2, Appendix A), the Agency concluded that the MOA information was of limited utility for understanding low-dose response within the context of the preponderance of human dose-response data near background levels of arsenic exposure. Please comment on the appropriateness of this approach. If additional MOA analyses are recommended, please describe in detail the feasibility of those analyses, what specifically they would entail, and why they would be considered more suitable evidence for informing dose-response analyses than the available epidemiological studies.
4. A primary recommendation of the NRC (2013) was, for well-studied priority health outcomes, to consider and incorporate information from multiple studies through the application of meta-analytic approaches to develop point estimates and confidence intervals. In response, EPA has developed a hierarchical, Bayesian meta-regression approach for the analysis of multiple epidemiologic studies (§5.3 and §5.4). Please comment on the clarity and scientific justification of this approach, as currently outlined.
    a. The EPA has converted a variety of exposure metrics to a common intake value as to include more studies in the dose-response analysis. Other studies in the open literature have limited dose-response to studies that measure exposure through drinking water. Please comment on EPA's common intake approach.
5. EPA will develop and apply a broad range of flexible dose-response models to investigate the dose-response relationships for cancer and non-cancer endpoints, including models that allow for non-linearity in low-dose regions (§5.3).

a. For non-cancer outcomes, EPA will develop traditional RfD and RfC values. These RFD or RfC values will preferably be derived using the Bayesian meta-regression methods (§5.3), but if that is infeasible due to data quality or poor model fits, a traditional BMD approach (i.e., selecting a single best model from individual dose-response datasets) will be used (§5.3). Is this modeling approach clearly outlined and scientifically justified?

b. EPA will derive, for priority cancer health outcomes, upper-bound U.S. population-specific risk estimates with confidence intervals from epidemiological data over a broad range of inorganic arsenic intake doses (µg/kg-day) above U.S. background levels (§5.3, §5.4). If the dose-response relationships are deemed sufficiently linear to background levels of exposure in the U.S., those linear relationships will be provided so that approximations of the mean and upper-bound lifetime extra risks for cancer health outcomes can be derived. The upper bound linear relationships will be analogous to oral slope factor (OSF) and inhalation unit risk (IUR) estimates that EPA has historically provided for cancer risks. In cases of non-linear dose-response relationships, flexible polynomial approximations will be provided. Please comment on whether this approach is sufficiently characterized and scientifically justified.

References

El-Masri, HA; Kenyon, EM. (2008). Development of a human physiologically based pharmacokinetic (PBPK) model for inorganic arsenic and its mono- and di-methylated metabolites. J Pharmacokinet Pharmacodyn 35: 31-68. http://dx.doi.org/10.1007/s10928-007-9075-z

NRC (National Research Council). (2013). Critical aspects of EPA's IRIS assessment of inorganic arsenic: Interim report. Washington, D.C: The National Academies Press.

U.S. EPA (U.S. Environmental Protection Agency). (2015). Assessment development plan for the Integrated Risk Information System (IRIS) toxicological review of inorganic arsenic. (EPA/630/R-14/101). Washington, D.C.: Office of Research and Development, NAS public meeting.