Systematic Review Methods and Hazard Characterization for the Updated Problem Formulation and Protocol for the Inorganic Arsenic (iAs) IRIS Assessment (Poster 1)

Janice S. Lee[1], Ila Cote[1], Tom Luben[1], Ellen Kirrane[1], Ryan Jones[1], Jeff Gift[1], J. Allen Davis[2], Ingrid Druwe[1], Audrey Turley[3], Michelle Cawley[3], Robyn Blain[3], Sorina Eftim[3], Kris Thayer[1]

[1] EPA, Office or Research and Development, National Center for Environmental Assessment – Research Triangle Park, [2] EPA, Office or Research and Development, National Center for Environmental Assessment – Cincinnati, [3] ICF International

Janice S. Lee | lee.janices@epa.gov | 919-541-9458

Purpose and Scope

- National Research Council (NRC) recommended that health outcomes be tiered and further prioritized given the volume of data on iAs, particularly human data (NRC, 2013).
- The 2019 updated problem formulation includes the refined scope that specifies which health outcomes are prioritized for dose-response analyses and toxicity value derivation.
- The protocol includes the methods and approaches proposed for use in developing the assessment, including systematic review and hazard characterization methods used to prioritize health outcomes.
- This poster presents diabetes as an illustrative example.

Prioritizing Health Outcomes

- NRC prioritized health outcomes into three tiers (NRC, 2013): Tier 1 (evidence of a causal association determined by other agencies and/or in published reviews); Tier 2 (other priority outcomes); Tier 3 (other endpoints to consider)
- EPA considered strength of the epidemiological evidence for hazard by
  - Relying on conclusions from assessments conducted by other health agencies (ATSDR, IARC, WHO, NTP) or
  - Conducting new systematic reviews of the existing literature.
- Epidemiology studies will be the focus of the assessment, consistent with prior NRC input.
  - Animals are not as sensitive to arsenic compared to humans due to interspecies metabolism differences.
  - Given the availability of low dose epidemiology studies, mechanistic data (which is largely based on animal and in vitro studies) is not considered critical for low dose extrapolation. However, as recommended by NRC, EPA inventoried mechanistic evidence (Protocol, Appendix A) and conducted MOA analyses to assess utility for reducing uncertainties in dose-response analysis (Poster 2). The analyses did not identify a clear application of the mechanistic evidence given the abundance of human studies.

Study Evaluation for Epidemiological Studies

- Risk of bias (RoB) was evaluated using questions adapted from OHAT (NTP, 2013) which considers study design, selection bias, confounding, exposure measures, outcome measures, and selective reporting.
- RoB was assessed for each study question using a four point scale that includes ratings of definitely low bias, probably low bias, probably high bias, and definitely high bias.

Strength of Evidence Judgements

- *Robust* and *Moderate* describe epidemiological evidence that supports a hazard. These terms are differentiated by the quantity and quality of information available to rule out alternative explanations for the results.
- *Slight* evidence includes situations in which there is some epidemiological evidence that supports a hazard, but there are substantial uncertainties in the data and a conclusion of *Moderate* does not apply.
- *Indeterminate* describes a situation where there are no epidemiological studies available for that evidence stream or the evidence is inconsistent and of low confidence, and cannot provide a basis for making a conclusion in either direction.
- *Compelling evidence of no effect* represents a situation where extensive epidemiological evidence across a range of populations and exposures identified no association. This scenario is rare.
- Both *slight* and *indeterminate* represent situations where the epidemiological evidence if insufficient to support a hazard, as uncertainty is too large.

U.S. Environmental Protection Agency
Office of Research and Development

The views expressed in this poster are those of the author(s) and do not necessarily represent the views or the policies of the U.S. Environmental Protection Agency.

Evidence Profile Table (diabetes example)

- An evidence profile table summarizes evidence integration conclusions.
- Approach supported in the National Academy of Sciences (NAS) review of implementation of systematic review in the IRIS Program (NAS, 2018).
- Tables are organized by study design (prioritizing designs with higher confidence studies) because studies of similar design generally possessed the same factors that increased or decreased confidence in the evidence base.

Studies (by design) and study confidence (i.e. based on risk of bias and sensitivity considerations[2])		Factors that increase confidence	Factors that decrease confidence	Summary of findings	Strength of evidence judgment
Cohort Studies	Studies were well-designed with well-characterized exposures, large number of subjects with long duration exposures, sufficient follow-up for latency, and used iterative and scientifically rigorous analyses; thus, they were generally interpreted with *high* or *medium* confidence Taiwan:Tseng et al. (2000), Chen et al. (2012), Hsu et al. (2013); United States: Ettinger et al. (2009); Denmark: Bräuner et al. (2014); Italy: D'Ippoliti et al., (2015)	• **Consistent** positive associations observed in populations across 3 continents, primarily at > 10 µg/kg-day • **Exposure-dependent** associations observed that establish **temporality** in studies in which prolonged arsenic exposure was associated with diabetes • **Low risk of bias** across the set of studies, due in part to well-characterized exposures • Exposure-response gradient observed across studies	• **Indirectness** with evaluation of metabolic syndrome and insulin sensitivity observed in one study • Small sample size in one study	The set of well-conducted studies report generally consistent, positive associations across diverse populations > 10 µg/kg-day , with some evidence for exposure-dependent changes within and across studies.	⊕⊕⊕ ROBUST Supported primarily by consistent and reliable evidence from cohort and case-control studies that rules out chance, confounding, and other biases with reasonable confidence. This evidence is based on associations generally observed above 10 µg/kg-day arsenic intake in general population studies across the world. Additional support is provided by consistent associations in both cross-sectional and ecological studies, although some uncertainties remain; this coherence across diverse study designs further strengthens the judgment.
Case-control Studies	Studies were generally well-designed with well-characterized exposures, included large population with adequate number of cases, precise case definition, and used iterative and scientifically rigorous analyses; thus, they were generally interpreted with *high* or *medium* confidence United States: James et al. (2013), Kim et al. (2013); Bangladesh: Pan et al. (2013b), Nizam et al. (2013); Mexico: Coronado-González et al. (2007);	• **Consistent** positive associations observed in populations across 3 continents, primarily at > 10 µg/kg-day	• Not all studies included individual-level exposure data	The set of well-conducted studies report generally consistent, positive associations across diverse populations at > 10 µg/kg-day, with some evidence for exposure-dependent changes	
Cross-sectional Studies	Studies were generally well-designed, with well-characterized exposures; however, some were limited by small sample size, interference of organic arsenicals in classifying exposure, or deficiency identifying cases, resulting in general interpretations of *medium* confidence United States: Gribble et al. (2012), Navas-Acien et al. (2008), Navas-Acien et al. (2009), Steinmaus et al. (2009); Korea: Rhee et al. (2013); Bangladesh: Islam et al. (2012); Mexico: Del Razo et al. (2011); Taiwan: Chen et al. (2011), Lai et al. (1994); South Korea: Kim and Lee (2011); China: Li et al. (2013), Feng et al. (2015); Canada: Feseke et al. (2015)	• **Consistent** positive associations observed in diverse populations across the world, although • **Exposure-dependent** associations observed across studies	• Series of studies conducted using NHANES data limited by authors' inability to interpret organic arsenic levels derived from seafood intake. Each author subsequently addressed it in their own way with differing results. • **Imprecision**: although consistent increases in odds ratios (or similar measures) were generally observed across studies, several did not find statistically significant increases, introducing uncertainty	A number of recent cross-sectional studies of populations across the world consistently reported a positive relationship between arsenic exposure and diabetes	
Ecological studies	Studies were limited to analyses in Taiwan and one study in United States and possessed some limitations in the quantitative characterization of exposure, leading to general interpretations of *medium* confidence Taiwan: Chiu et al. (2006); Tsai et al. (1999); Wang et al. (2003); United States: Meliker et al. (2007)	• **Consistent** positive associations observed	• Some **concern for risk of bias** across the set of studies, due largely to deficiencies in exposure assessment and inability to account for potential confounding from individual-level variables • Limited number of studies, primarily only in one population	Few ecological studies with majority looking at diabetes mortality that provide consistent positive associations.	

References can be found in HERO (https://hero.epa.gov/hero/index.cfm/project/page/project_id/2211)

Characterization of Hazard

Health outcome	NRC Tier	EPA strength-of-evidence judgement of human evidence of a causal association
NRC Tiers: Tier 1: Evidence of causality; Tier 2: Other priority outcome; Tier 3: Other endpoints to consider		
Lung cancer	Tier 1	Robust. Based on NRC Tier 1 and conclusions of "carcinogenic" for lung cancer from other assessments (ATSDR, 2016; NTP, 2016; IARC, 2012; WHO, 2011a, b; ATSDR, 2007; IARC, 2004b).
Bladder cancer	Tier 1	Robust. Based on NRC Tier 1 and conclusions of "carcinogenic" for bladder cancer from other assessments (ATSDR, 2016; NTP, 2016; IARC, 2012; WHO, 2011a, b; ATSDR, 2007; IARC, 2004b).
Skin cancer	Tier 1	Robust. Based on 1995 EPA conclusion of "known carcinogen" based on skin cancer (U.S. EPA, 1995), NRC Tier 1, and conclusions of "carcinogenic" for skin cancer based on other assessments (ATSDR, 2016; NTP, 2016; IARC, 2012; WHO, 2011a, b; ATSDR, 2007).
Ischemic heart disease	Tier 1	Robust. Based on systematic review conducted by EPA on diseases of the circulatory system (ischemic heart disease and hypertension/stroke), which is similar to associations noted in other assessments (ATSDR, 2016; WHO, 2011a, b; ATSDR, 2007) and meta-analysis[a] (Moon et al., 2017a, b; Moon et al., 2013).
Skin lesions	Tier 1	Robust. Based on NRC Tier 1 and conclusions from other assessments (ATSDR, 2016; WHO, 2011a, b; ATSDR, 2007).
Diabetes	Tier 2	Robust. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016), an expert review conducted as part of an NTP workshop (Maull et al., 2012; Thayer et al., 2012) and a meta-analysis[a] (Wang et al., 2014).
Pregnancy outcomes (fetal and infant morbidity)	Tier 2	Robust. Based on systematic review conducted by EPA on pregnancy and birth outcomes (fetal growth, prematurity, and infant growth in the first 5 yr of life), which is similar to associations noted in ATSDR (2016) and meta-analysis[a] by Quansah et al. (2015).
Pregnancy outcomes (fetal loss, stillbirth, and neonatal mortality)	Tier 3	Robust. Based on systematic review conducted by EPA on pregnancy and birth outcomes (fetal loss and infant mortality in the first 5 yr of life), which is similar to associations noted in ATSDR (2016), review by Bloom et al. (2010), and a meta-analysis[a] by Quansah et al. (2015).
Hypertension/ stroke[b]	Tier 3	Robust. Based on systematic review conducted by EPA on diseases of the circulatory system (including ischemic heart disease and hypertension/stroke), which is similar to associations noted in ATSDR (2016), review by Abhyankar et al. (2012), and meta-analysis[a] (Moon et al., 2017a, b; Moon et al., 2013).
Renal cancer	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b) and ATSDR (2016).
Nonmalignant respiratory disease	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).
Neurodevelopmental toxicity	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).
Immune effects	Tier 2	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).
Liver cancer	Tier 3	Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b).
Health outcomes considered to have slight evidence		
Prostate cancer	Tier 2	Slight. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b).
Pancreatic cancer	Tier 3	Slight. Based on systematic review conducted by EPA and associations noted in IARC (2004b).
Renal disease	Tier 3	Slight. Based on systematic review conducted by EPA.

[a]In cases of Tier 2 or 3 health outcomes, the results and conclusions of systematic reviews conducted by EPA formed the primary rationale for identifying a health outcome as having robust, moderate, or slight strength of evidence. For health outcomes that also had meta-analyses conducted by outside groups, the meta-analyses are considered supplemental information. Relevant primary studies included in the meta-analyses were considered in the systematic reviews conducted by EPA.

[b]These outcomes considered along with the larger ischemic heart disease database; the strength of the epidemiologic database was based on the full set of all studies for all endpoints.

Note: The results of the systematic reviews and hazard analyses will be included in the assessment and subject to external peer review (or cited, if published in the peer review literature).

Conclusions

- Health outcomes with robust or moderate evidence were prioritized for dose-response
- Prostate cancer, pancreatic cancer, and renal disease were not prioritized (slight evidence)
- Immune effects not prioritized (no suitable data sets for analysis)
- Prioritization of health outcomes for dose-response analysis is summarized in Table 5-3 of the protocol