EPA
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Environmental Protection
Agency

Updated Problem Formulation and Scoping

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Outline for Today's Presentations

- Introduction and Role of the Protocol in the IRIS Systematic Review Process
- **Updated Problem Formulation and Scoping**
- Systematic Review Methods Used to Prioritize Health Outcomes
- Dose-Response Assessment and Derivation of Slope Factors and Reference Values

History of the IRIS Toxicological Review of Inorganic Arsenic

- **1988:** EPA published IRIS Toxicological Review of Inorganic Arsenic
- **1999,2001:** NRC, at EPA's request, published *Arsenic in Drinking Water* and *Update*
- **2005:** Draft released
- **2010:** Draft released and reviewed by Science Advisory Board (SAB)
- **2011:** Congress directed EPA to contract with NRC to review assessment
- **2013:** EPA held public planning and scoping meetings, webinars, released draft Assessment Development Plan (ADP) and preliminary materials for NRC review
- **2013:** NRC released interim report, *Critical Aspects of EPA's IRIS Assessment of iAs* and provided recommendations; NRC supported EPA's plan
- **2014:** EPA held a public science meeting to present and encourage comments on the ADP, preliminary materials, and key science issues
- **2015:** EPA briefed the NRC on revised draft Assessment Development Plan with updated dose-response approaches
- **2019:** EPA released the protocol for public comment and NRC review

Past major conclusions and recommendations from the NRC (2013-2015)

- Health outcomes should be tiered and further prioritized
- Animal and mechanistic data considered as supporting evidence
- Conduct dose-response analysis for causal or likely causal relationships, even in absence of understanding the potential MOAs
- If the epidemiological data in the range of observation is inadequate, then the mode of action (MOA) data should be used to the extent possible to extrapolate below the observed range
- Conduct MOA analyses to determine whether the available MOA evidence can inform dose-response of health outcomes
- Dose-response meta-analysis approach for epidemiological studies
- Use of PBPK model (El-Masri and Kenyon, 2008) to understand the relationship between drinking water and urinary concentrations of arsenic

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

Scoping Summary

Table 2-1. EPA program office or region interest in the inorganic arsenic assessment

EPA program or regional office	Oral	Inhalation	Statutes/regulations and executive orders
Office of Land and Emergency Management Regions 1-10	✓	✓	Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Resource Conservation and Recovery Act (RCRA)
Office of Water	✓		Safe Drinking Water Act (SDWA) and Clean Water Act (CWA)

Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment (EPA, 2019)

Problem Formulation Updates

- Developed an updated problem formulation and protocol document that presents adjustments to the 2015 draft Assessment Plan (U.S. EPA, 2015)
- The refined scope was informed by prior science discussions with the National Research Council (NRC), EPA program and regional offices, and other stakeholders. 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
  - NAS concluded that human data are expected to be the basis for dose-response analyses (NRC, 2013)
  - 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

NRC (National Research Council). (2013). Critical aspects of EPA's IRIS assessment of inorganic arsenic: Interim report. Washington, DC: The National Academies Press. https://www.nap.edu/catalog/18594/critical-aspects-of-epas-iris-assessment-of-inorganic-arsenic-interim

Approach to Prioritize Health Outcomes

Basis:

- Started with 2013 NRC Tiering
  - Tier 1: evidence of a causal association determined by other agencies and/or in published systematic reviews
  - Tier 2: other priority outcomes
  - Tier 3: other endpoints to consider
- NRC recommended EPA conduct additional analyses to further refine their tiering
- EPA prioritized health outcomes by accepting conclusions from other health agencies (ATSDR, NTP, IARC, WHO) on bladder cancer, lung cancer, skin cancer, and skin lesions; and by conducting new systematic reviews

Prioritized Health Outcomes

Table 2-2. Strength of evidence judgements to help prioritize health outcomes of concern for EPA's inorganic arsenic assessment

Health outcome	NRC tier (NRC, 2013)	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 or review articles (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).

Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment (EPA, 2019)

Prioritized Health Outcomes (continued)

Table 2-2. Strength of evidence judgements to help prioritize health outcomes of concern for EPA's inorganic arsenic assessment

Health outcome	NRC tier (NRC, 2013)	EPA strength-of-evidence judgement of human evidence of a causal association
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.

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Health outcomes with *robust* or *moderate* evidence were identified for potential dose-response analyses

Mode of Action (MOA) Analyses

- MOA analyses can be used to address human relevance, differences in response among humans, and to inform dose-response relationships (EPA Cancer Guidelines, 2005)
  - Human relevance: inorganic arsenic is a known carcinogen with a large amount of epidemiological evidence with carcinogenic risk to humans established by IARC (Group 1 carcinogen- carcinogenic to humans)
  - Interhuman variability: extensive information on risk modifiers in numerous epidemiological studies
  - Dose-response: abundance of epidemiological studies of low level exposure to inorganic arsenic
- Considerable efforts undertaken to conduct MOA analyses to determine whether the available MOA evidence can inform dose-response of health outcomes
- Appendix A: Analysis of modes of action common to multiple health effects
  - reactive oxygen species (ROS) generation and oxidative stress responses, As(III) binding to thiol groups and inhibition of key enzymes, As(V) inhibition of oxidative phosphorylation, cell cycling and damage repair impairment, epigenetics, endocrine disruption, cytotoxicity and regenerative proliferation
  - ~5726 studies screened, 191 studies summarized in appendix A
- Case study using bladder cancer to address feasibility of using MOA and mechanistic data to inform dose-response (see Poster 2)

Mode of Action (MOA) Case Study

APPENDIX A. ANALYSIS OF MODES OF ACTION COMMON TO MULTIPLE HEALTH EFFECTS

A.1. BACKGROUND

EPA defines mode of action (MOA) as "a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation [or other adverse outcomes]" (U.S. EPA, 2005a). The principles of the 2001 World Health Organization's (WHO's) International Programme on Chemical Safety (IPCS) Framework were incorporated into the EPA 2005 Cancer Guidelines. In addition to the IPCS principles, EPA Cancer Guidelines also incorporated standards from the *Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action*, published by members of the International Life Sciences Institute Risk Science Institute (Meek et al., 2003). These principles are outlined in Section 2.4; MOA Framework Guidelines of the EPA Cancer Guidelines document and provide guidance for developing MOA analyses. The guidelines state that "mode of action conclusions should be [are] used to address the question of human relevance of animal tumor responses, to address differences in anticipated response among humans, such as between children and adults or men and women; and as the basis of decisions about the anticipated shape of the dose-response relationship" [see Sections 2.4.2.2 and 2.4.3.4 of U.S. EPA (2005a)].

The Integrated Risk Information System (IRIS) Program routinely conducts MOA analyses to inform hazard identification and dose-response analysis, but a complete understanding of MOA is not required to develop hazard conclusions or toxicity values. In the case of arsenic, the National Research Council (NRC) recommended EPA conduct MOA analyses to facilitate understanding of exposure-response relationships and interindividual variabilities for health outcomes where extrapolation to below the observed range may be necessary. However, the NRC also recognized that it was not clear whether such an analysis would be feasible.

A MOA analysis was considered less effective for hazard characterization given the abundance of epidemiological evidence, including at low levels of exposure, and recognition that data from animal studies of inorganic arsenic are of limited applicability for dose-response analysis in human health risk assessment (ATSDR, 2007).

This appendix describes the analyses conducted by EPA to characterize MOAs associated with arsenic exposure, focusing on MOAs common to multiple adverse health effects versus tissue-specific descriptions. As will become evident, recognized MOAs for any of the hypothesized bases for inorganic arsenic (iAs)-induced disease are incomplete, poorly populated with key events, and/or nonspecific. This prevents a critical evaluation of dose-response relationships, particularly in the low-dose region.

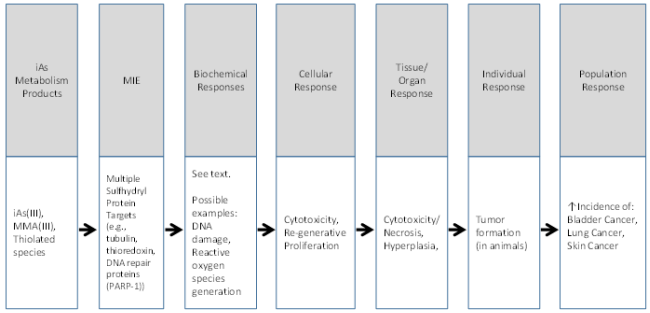

Figure A-4. Hypothesized mode of action for cytotoxicity and regenerative proliferation.

Table A-1. Data on effects mediated by cytotoxicity and regenerative proliferation – relevant health effects: bladder, lung, and skin cancer

Key events	Observations	Organ system	Test system	Dose (exposure duration)[a]	References
Molecular initiating events					
Reactions with GSH and other nonprotein thiols	Glutathione, cysteine, lipoic acid conjugates	Many	Humans, rodents, in vitro	Environmentally relevant and higher exposures	Cohen et al. (2013)
Reaction with thiols/dithiols in specific proteins	Inorganic arsenic binding with tubulin, keratin, ERα and related receptors, PARP-1, thioredoxin reductase, ASSMT, KEAP-1, many studies of zinc finger proteins, peptides; IκB kinase; EGFR, Shc; tyrosine phosphatases, ubiquitination enzymes; XPA, XPD (NER enzymes)	Not applicable	In vitro binding of As(III) to synthetic peptides	Kds = ~1–30 μg/L (↓ Kd with ↑ cysteine residues)	Kitchin and Wallace (2008, 2005); Qin et al. (2008)
	Reduced PARP activity, restored by coincubation with Zn	Urothelium (human)	UROtsa cells	50 nM MMA(III) (12–52 wk)	Wnek et al. (2011); Wnek et al. (2009)
Biochemical responses					
See summary text					Cohen et al. (2013)
Cellular responses					
Cytotoxicity/viability	24-h viability (mitochondrial dehydrogenase assay)	Urothelium (human)	UROtsa, other cell lines	Arsenite IC_{50} for UROtsa = 17.8 μM, 3.2 μM for bronchial	Styblo et al. (2000)

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Poster 2

- While the MOA evaluation provided additional support by identifying arsenic-specific mechanisms and risk modifiers likely to increase risk of human bladder cancer, the impact and utility of mechanistic information on dose-response analyses was minimal, especially given the abundance of epidemiology studies of low-level exposure

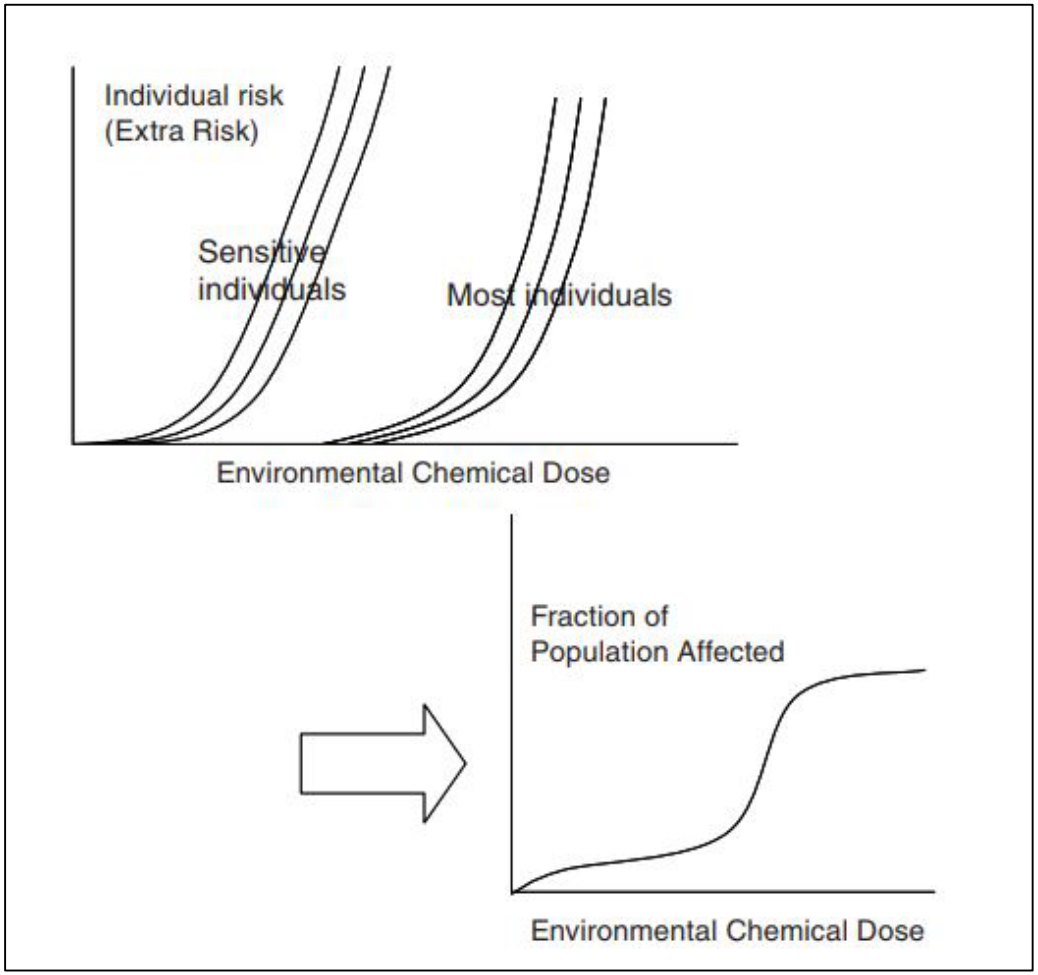
Challenges in Using Mode of Action (MOA) Analyses

- Mechanisms of arsenic-associated disease induction are complex, inter-related, differentially applicable to cancer and noncancer outcomes, and likely interoperable in different ways across the concentration ranges tested
- Little evidence that directly addresses this complexity in the low-dose region
- Much of the primary evidence is based on in vitro studies conducted at high concentrations
- Assumptions of applicability of in vitro model systems to human response and ability to extrapolate in vitro concentrations to human exposure levels
- Mechanistic evidence also comes from rodent studies, which are less sensitive to arsenic compared to humans due to interspecies physiological differences

Challenges in Using Mode of Action (MOA) Analyses- Lessons Learned from Case Study

Hypothesized MOAs relevant to bladder cancer	Challenges
ROS generation and oxidative stress	• Use of different cell lines (e.g., primary & immortalized) • Differences in experimental design used to measure outcome (e.g. ROS) • Differences in response (mouse vs rat vs human derived cell systems vs rodent in vivo studies) • Differences in concentration that elicits response within studies depending on outcome being measured
iAs binding to thiol groups & inhibition of key enzymes	
As(V) inhibition of oxidative phosphorylation	
Epigenetics	
Cytotoxicity & regenerative proliferation	

Challenges in Using Mode of Action (MOA) Analyses



NRC, 2009

- Different populations will have different sensitivities to each key event in an MOA
- Widely differing sensitivity can create a sigmoidal shaped, bimodal distribution of risk

Summary

- Human studies are basis for hazard conclusions and dose-response analyses
- The impact and utility of mechanistic information on dose-response analyses was extensively evaluated but considered to have minimal impact on dose-response given the abundance of epidemiology studies of low-level exposure for all outcomes with robust or moderate evidence
- The following outcomes were identified for potential dose-response analyses based on a determination of *robust* or *moderate* evidence:
  - Cancers of the bladder, lung, kidney, liver and skin
  - Noncancer effects on the circulatory system, reproductive system, developmental system, endocrine system, immune system, respiratory system, and skin
- Outcomes with slight evidence are not considered further
  - Prostate and pancreatic cancers
  - Renal disease

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