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

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

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

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

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**

<table>
<thead>
<tr>
<th>Health outcome</th>
<th>NRC tier (NRC, 2013)</th>
<th>EPA strength-of-evidence judgement of human evidence of a causal association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRC Tiers: Tier 1: Evidence of causality; Tier 2: Other priority outcome; Tier 3: Other endpoints to consider</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Tier 1</td>
<td>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).</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Tier 1</td>
<td>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).</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Tier 1</td>
<td>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).</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>Tier 1</td>
<td>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 (Moon et al., 2017a, b; Moon et al., 2013).</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Tier 1</td>
<td>Robust. Based on NRC Tier 1 and conclusions from other assessments (ATSDR, 2016; WHO, 2011a, b; ATSDR, 2007).</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Tier 2</td>
<td>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 (Maul et al., 2012; Thayer et al., 2012) and a meta-analysis (Wang et al., 2014).</td>
</tr>
<tr>
<td>Pregnancy outcomes (fetal and infant morbidity)</td>
<td>Tier 2</td>
<td>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 by Quansah et al. (2015).</td>
</tr>
<tr>
<td>Pregnancy outcomes (fetal loss, stillbirth, and neonatal mortality)</td>
<td>Tier 3</td>
<td>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 by Quansah et al. (2015).</td>
</tr>
<tr>
<td>Hypertension/stroke &lt;sup&gt;b&lt;/sup&gt;</td>
<td>Tier 3</td>
<td>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 (Moon et al., 2017a, b; Moon et al., 2013).</td>
</tr>
</tbody>
</table>
Prioritized Health Outcomes (continued)

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

<table>
<thead>
<tr>
<th>Health outcome</th>
<th>NRC tier (NRC, 2013)</th>
<th>EPA strength-of-evidence judgement of human evidence of a causal association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cancer</td>
<td>Tier 2</td>
<td>Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b) and ATSDR (2016).</td>
</tr>
<tr>
<td>Nonmalignant respiratory disease</td>
<td>Tier 2</td>
<td>Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).</td>
</tr>
<tr>
<td>Neurodevelopmental toxicity</td>
<td>Tier 2</td>
<td>Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).</td>
</tr>
<tr>
<td>Immune effects</td>
<td>Tier 2</td>
<td>Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in ATSDR (2016).</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Tier 3</td>
<td>Moderate. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b).</td>
</tr>
</tbody>
</table>

Health outcomes considered to have slight evidence

<table>
<thead>
<tr>
<th>Health outcome</th>
<th>NRC tier (NRC, 2013)</th>
<th>EPA strength-of-evidence judgement of human evidence of a causal association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>Tier 2</td>
<td>Slight. Based on systematic review conducted by EPA, which is similar to associations noted in IARC (2012, 2004b).</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Tier 3</td>
<td>Slight. Based on systematic review conducted by EPA and associations noted in IARC (2004b).</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Tier 3</td>
<td>Slight. Based on systematic review conducted by EPA.</td>
</tr>
</tbody>
</table>

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

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

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

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

- 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.

NRC, 2009
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
Acknowledgements

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