



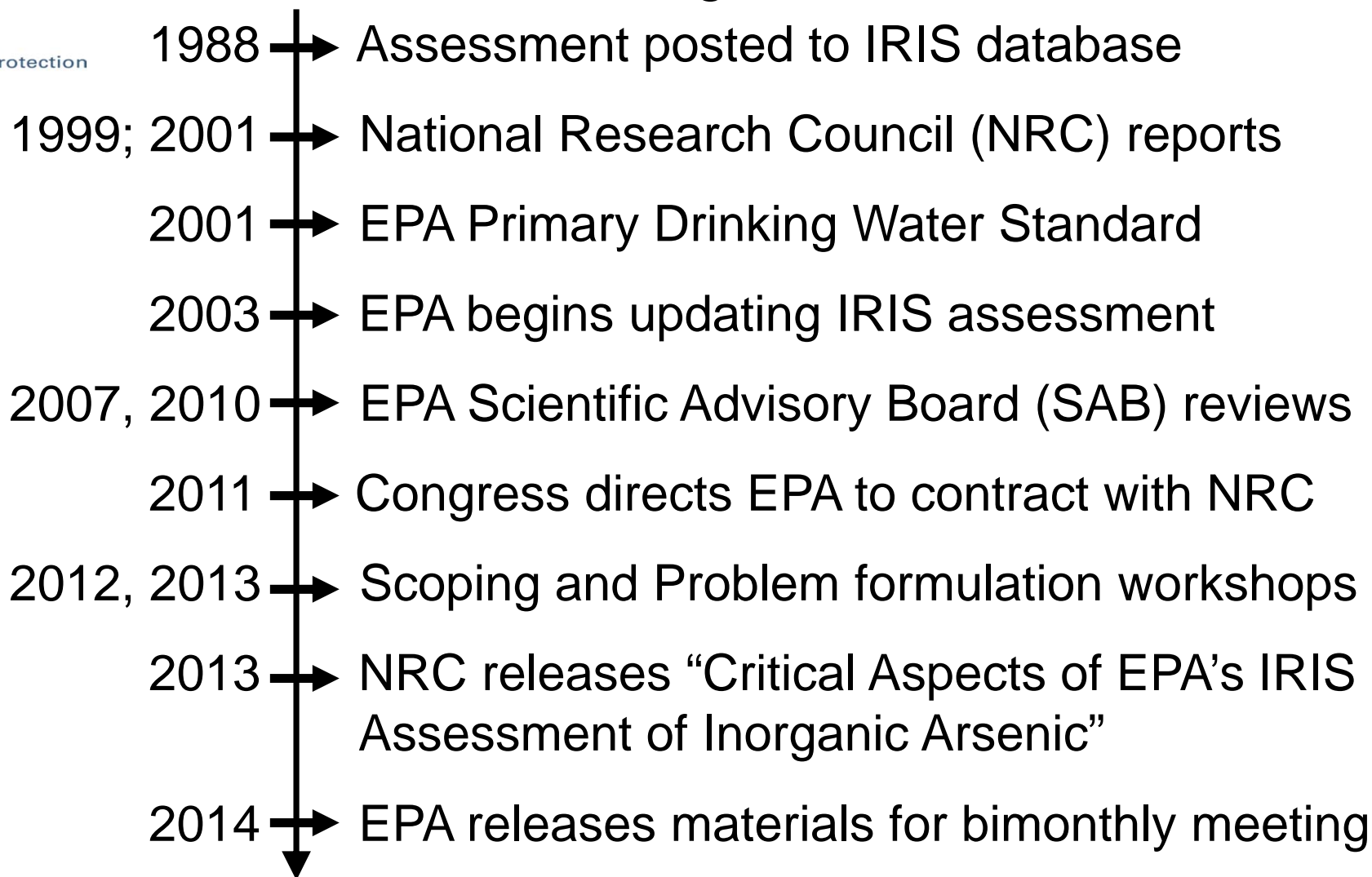
IRIS June Bimonthly Public Meeting

June 25-27, 2014





IRIS Efforts on Inorganic Arsenic



Outline

1. Context

2. Content

3. Concept

4. Contact



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Feedback from the NRC 2013 Interim Report

- Documents clearly reflect previous NRC recommendations and outline an improved approach
- Materials reflect input collected from program and regional offices and public stakeholders
- Example evidence tables capture salient information on epidemiology studies
- NRC supported approach for causal determination
- NRC supported plan to perform MOA analyses for causal or likely causal health outcomes
- NRC agreed with proposal to use probabilistic approaches to consider uncertainty and variability



Preliminary Materials for Bimonthly Meeting

Outline

- 1. Context
- 2. Content
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NRC/Stakeholder Recommendation	Preliminary Material Prepared
Problem Formulation	Section 1 – Assessment Development Plan
Literature Search Strategy and Selection Criteria	Section 2 – Literature Search Strategy Section 8 – MOA Literature Search Strategy
Literature Search Results	Section 3 – Literature to Support Hazard ID
Risk of Bias	Section 4 – Risk of Bias Evaluations – epi Section 6 – Risk of Bias Evaluations – tox
Evidence Tables	Section 5 – Evidence tables – epi Section 7 – Evidence tables – tox
Modes of Action	Section 9 – MOA Hypothesis Summaries
AOP Framework	Section 10 –Mechanistic Data Tables



What's coming up for IRIS and arsenic?

Proposed Next Steps	Proposed Date
Problem Formulation/Hazard ID – discussion of key science issues	Today/ Tomorrow
Public webinar – Proposed approaches for dose-response and meta-analyses	July 2014
Public webinars – Hazard ID synthesis sections	Fall 2014
Internal Agency Review	Fall 2014
Interagency Science Consultation	Winter 2015
Public meeting on draft assessment	Winter 2015
NRC External Peer Review	Spring 2015

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<http://www.epa.gov/iris/irisworkshops/arsenic/index.htm>



Outline

1. Context
2. Content
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- 4. Contact**

Where can I get information?

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- Vincent Cogliano: Cogliano.Vincent@epa.gov

NCEA RTP Deputy Division Director - *Acting*

- Reeder Sams: Sams.Reeder@epa.gov

Co-Chemical Managers for IRIS Assessment

- Janice Lee: Lee.JaniceS@epa.gov
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Inorganic Arsenic Website

<http://www.epa.gov/iris/irisworkshops/arsenic/index.htm>

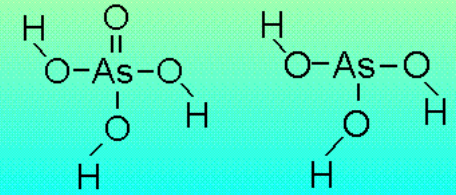
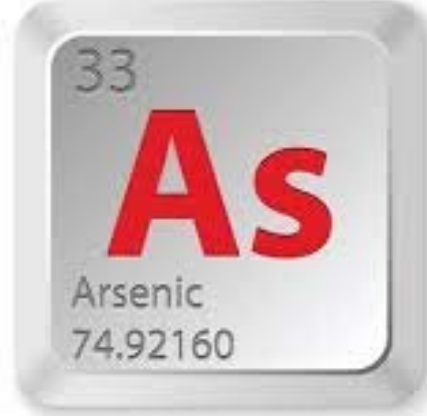
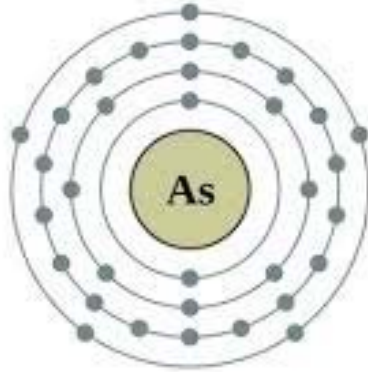
Inorganic Arsenic Science Issues

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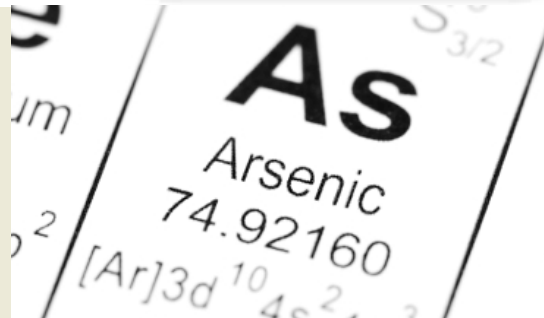
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Key Science Issues for Inorganic Arsenic

- 1) Application of NRC recommendations**
- 2) Risk-of-bias approach**
- 3) Integrating results of epidemiologic studies**
- 4) Concordance of effects between human and animals**
- 5) Upstream biological events for clinical disease endpoints**
- 6) Mode-of-action and adverse outcome pathways**
- 7) In-utero exposure leading to disease later in life**
- 8) Implications of nutritional factors on internal dose and response**



Inorganic Arsenic Science Issue 1: Application of NRC recommendations

Relevant Materials

Section 1 -
Assessment
Development Plan

Section 2 –
Literature Search
Strategy and
Systematic Review

**Science and
Decisions** (NRC
2009)

**Interim report on
iAs** (NRC 2013)

**Review of EPA's
IRIS Process**
(NRC 2014)

The preliminary material include an Assessment Development Plan (Section 1) that characterizes scoping, problem formulation, and the overarching approach for the IRIS assessment.

EPA is seeking public discussion on the structure and utility of the Assessment Development Plan and whether it has appropriately applied the recommendations from NRC (2013), *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report*.



Inorganic Arsenic Science Issue 1: Application of NRC recommendations

NRC Recommendations

1. Implement planning and scoping

2. Implement problem formulation
3. Implement systematic review
4. Implement evidence integration

Discussion Points

- Opportunities for Agency partner and public stakeholder input
- Responsiveness of planning and scoping summary statement
- Incorporation of Agency partner and public stakeholder recommendations



Inorganic Arsenic Science Issue 1: Application of NRC recommendations

NRC Recommendations

1. Implement planning and scoping
- 2. Implement problem formulation**
3. Implement systematic review
4. Implement evidence integration

Discussion Points

- Adaptation of ecological-based approach to problem formulation for IRIS (e.g., sources, stressors, receptors)
- Conceptual model assessment parameters
- Analysis plan revisions



Inorganic Arsenic Science Issue 1: Application of NRC recommendations

NRC Recommendations

1. Implement planning and scoping
2. Implement problem formulation
- 3. Implement systematic review**
4. Implement evidence integration

Discussion Points

- Literature search strategy
- Natural language processing
- Systematic review and resources



Inorganic Arsenic Science Issue 1: Application of NRC recommendations

NRC Recommendations

1. Implement planning and scoping
2. Implement problem formulation
3. Implement systematic review
- 4. Implement evidence integration**

Discussion Points

- Causal framework for hazard identification



Inorganic Arsenic Science Issue 2: Risk of bias approach

Relevant Materials

Section 2 – Literature Search Strategy and Systematic Review

Section 4 – Risk of bias evaluations for epi

Section 6 – Risk of bias evaluations for tox

This assessment uses an approach for evaluating risk-of-bias in human and animal studies.

EPA is seeking public discussion on the transparency, appropriateness, and utility of the risk-of-bias approach.



Inorganic Arsenic Science Issue 2: Risk-of-bias approach

NRC Recommendation

1. Evaluate risk of bias using established guidelines

Discussion Points

- Implementation of modified OHAT approach
- Risk of bias and study quality
- External validity and fit-for-purpose evaluation
- Using risk of bias to inform data selection



Inorganic Arsenic Science Issue 3: Integrating results of epidemiologic studies

Relevant Materials

Section 5 – Evidence tables for epi

The epidemiologic studies have employed different approaches to exposure characterization, resulting in different dose metrics.

EPA is seeking public discussion on approaches it can use to evaluate health effect information across epidemiologic studies.



Inorganic Arsenic Science Issue 3: Integrating results of epidemiologic studies

NRC Recommendations

1. Strength of evidence characterized with respect to modified Hill criteria

2. Common exposure metric needed to integrate across studies
3. Perform meta-analysis for hazard identification if ≥ 3 peer reviewed studies
4. Examine studies providing both exposure and biomarker data; crucial to assess exposure on individual level

Discussion Points

- Primary and secondary literature
- Causal determination framework



Inorganic Arsenic Science Issue 3: Integrating results of epidemiologic studies

NRC Recommendations

1. Strength of evidence characterized with respect to modified Hill criteria
- 2. Common exposure metric needed to integrate across studies**
- 3. Perform meta-analysis for hazard identification if ≥ 3 peer reviewed studies**
4. Examine studies providing both exposure and biomarker data; crucial to assess exposure on individual level

Discussion Points

- Considerations for selecting common exposure metric
- Comparing studies using different exposure groups or quartiles
- Considerations for study selection meta-analysis
- Utility of meta-analysis for hazard identification and causal determination



Inorganic Arsenic Science Issue 3: Integrating results of epidemiologic studies

NRC Recommendations

1. Strength of evidence characterized with respect to modified Hill criteria
2. Common exposure metric needed to integrate across studies
3. Perform meta-analysis for hazard identification if ≥ 3 peer reviewed studies
- 4. Examine studies providing both exposure and biomarker data; crucial to assess exposure on individual level**

Discussion Points

- Ecological studies
- Exposure data and biomarkers – considerations for PBPK modeling
- Consideration of exposure metrics for evidence integration



Inorganic Arsenic Science Issue 4: Concordance of effects between human and animals

Relevant Materials

Section 3 –
Summary of
literature identified
Section 7 - Evidence
tables for tox

NRC (2013) identified a tiered set of health effects for inorganic arsenic.

EPA is seeking public discussion on whether animal studies on each endpoint are informative of the potential for similar effects in humans.



Inorganic Arsenic Science Issue 4: Concordance of effects between human and animals

NRC Recommendations

1. Hazard assessment should include epi and experimental evidence and integrate MOA where possible

Discussion Points

- Considerations for using toxicological data to inform human relevance of observed effects
- Dose considerations for evaluating concordance between animal and human data
- Considerations for evaluating differences in health outcomes between humans and animals



Inorganic Arsenic Science Issue 5: Upstream biological events for clinical disease endpoints

Relevant Materials

Section 5 –Evidence tables for epi.

Section 7 - Evidence tables for tox

NRC (2013) identified a tiered set of health effects for inorganic arsenic.

EPA is seeking public discussion to identify upstream biological events (in humans or in animals) that can be used as markers for each of these clinical disease endpoints.



Inorganic Arsenic Science Issue 5: Upstream biological events for clinical disease endpoints

NRC Recommendations

- 1. Hazard assessment should include epi and experimental evidence and integrate MOA where possible**
- 2. Consider dose and time-dependence of exposure to key events**

Discussion Points

- Considerations for establishing upstream events as markers of human disease
- Dose considerations for upstream events
- Considerations for establishing health endpoints as indicators of disease progression



Inorganic Arsenic Science Issue 6: Mode-of-action and adverse outcome pathways

Relevant Materials

Section 9 – MOA hypothesis summaries

Section 10 – Preliminary mechanistic tables

The preliminary materials include mode-of-action summaries and mechanistic data tables intended to facilitate subsequent development of adverse outcome pathways for the health effects of inorganic arsenic. ***(EPA is presenting this material to stimulate public discussion and has not yet conducted mode-of-action or adverse-outcome-pathway analyses).***

EPA is seeking public discussion on (1) the transparency and utility of the mode-of-action summaries and mechanistic data tables, (2) how mechanistic data can inform the hazard identification and dose-response analysis for each hazard, (3) specific hypothesized modes-of-action for the dose-response analysis for each hazard, and (4) whether there are other modes-of-action that warrant consideration.



Inorganic Arsenic Science Issue 6: Mode-of-action and adverse outcome pathways

NRC Recommendations

- 1. Hazard assessment should include epi and experimental evidence and integrate MOA where possible**
2. MOA analysis needs to consider there may be multiple mechanisms for bladder cancer
3. EPA should design MOA tables
4. Important to clearly present strengths and weaknesses of evidence of MOA(s) for each observed health outcome
5. Identifying MOA gaps is important

Discussion Points

- Considerations for evaluating mechanistic data for hazard identification



Inorganic Arsenic Science Issue 6: Mode-of-action and adverse outcome pathways

NRC Recommendations

1. Hazard assessment should include epi and experimental evidence and integrate MOA where possible
- 2. MOA analysis needs to consider there may be multiple mechanisms for bladder cancer**
- 3. EPA should design MOA tables**
4. Important to clearly present strengths and weaknesses of evidence of MOA(s) for each observed health outcome
5. Identifying MOA gaps is important

Discussion Points

- Additional MOAs that should be considered in hazard identification
- MOAs which should not be evaluated in hazard identification
- Preliminary MOA table format
- Considerations for MOA analyses related to susceptibility (e.g., life-stage)



Inorganic Arsenic Science Issue 6: Mode-of-action and adverse outcome pathways

NRC Recommendations

1. Hazard assessment should include epi and experimental evidence and integrate MOA where possible
2. MOA analysis needs to consider there may be multiple mechanisms for bladder cancer
3. EPA should design MOA tables
4. **Important to clearly present strengths and weaknesses of evidence of MOA(s) for each observed health outcome**
5. **Identifying MOA gaps is important**

Discussion Points

- Approaches for AOP analyses
- Decision points for MOA analysis
- Clear presentation of data gaps



Inorganic Arsenic Science Issue 7: In-utero exposure leading to disease later in life

Relevant Materials

Section 9 – MOA hypothesis summaries

Section 10 – Preliminary mechanistic tables

Human and animal studies suggest that in-utero exposure to inorganic arsenic may contribute to subsequent development of disease later in life.

EPA is seeking public discussion to identify approaches that can be used to evaluate these studies for hazard identification and subsequent dose-response analysis.



Inorganic Arsenic Science Issue 7: In-utero exposure leading to disease later in life

NRC Recommendations

- 1. Evaluate whether early life exposure may affect risk of arsenic-related effects in adults**
- 2. Essential to evaluate potential adverse effects on fetal and postnatal exposure to inorganic arsenic**

Discussion Points

- Considerations for interpreting whole-life exposure in terms of potential in utero susceptibility
- Hypothesized MOAs that may inform hazard identification of in utero exposures
- Comparing effects of in utero exposures in humans and animals



Inorganic Arsenic Science Issue 8: Implications of nutritional factors in internal dose and response

Topic added based upon following comment from public stakeholder.

Relevant Materials

- Section 1** – Assessment Development Plan
- Section 9** – MOA hypothesis summaries
- Section 10** – Preliminary mechanistic tables

Exposure assessment for study populations compared to the United States population. Populations exposed to high arsenic levels in well water in countries such as Bangladesh and West Bengal also receive increased inorganic arsenic exposure because of their diet and cooking practices as well as from crops grown using contaminated water. In addition, many issues should be considered in assessing exposure to inorganic arsenic when using urinary arsenic levels. In particular, total arsenic in urine is confounded by organic arsenic compounds from the diet. Arsenic species in urine such as DMA may arise from inorganic arsenic methylation as well as directly from its presence in the diet or from ingestion of arsenosugars or other dietary precursor compounds.

Susceptibility to arsenic toxicity and the dose-response relationship may be affected by a number of factors that enhance arsenic toxicity as well as independently increase risk of various diseases (e.g., nutritional deficiencies, smoking, and betel nut use are very important factors for Bangladesh).



Inorganic Arsenic Science Issue 8: Implications of nutritional factors in internal dose and response

NRC Recommendations

- 1. Assessment should consider nutritional status of study populations when examining dose-response relationships**
- 2. Evaluation of size/nature of vulnerable populations will help determine if epi studies adequately capture these groups**
- 3. Examine susceptible groups of the population**

Discussion Points

- Ability of mechanistic data to inform susceptibility
- Identification of susceptibility factors
- Criteria for quantitative evaluations of susceptibility factors