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Hazard Identification for the IRIS Toxicological Review of Inorganic Arsenic

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Outline for Today's Presentations

- Introduction
- Systematic Review
- **Hazard Identification**
- Adverse Outcome Pathways
- Toxicokinetics
- Dose-Response Methods

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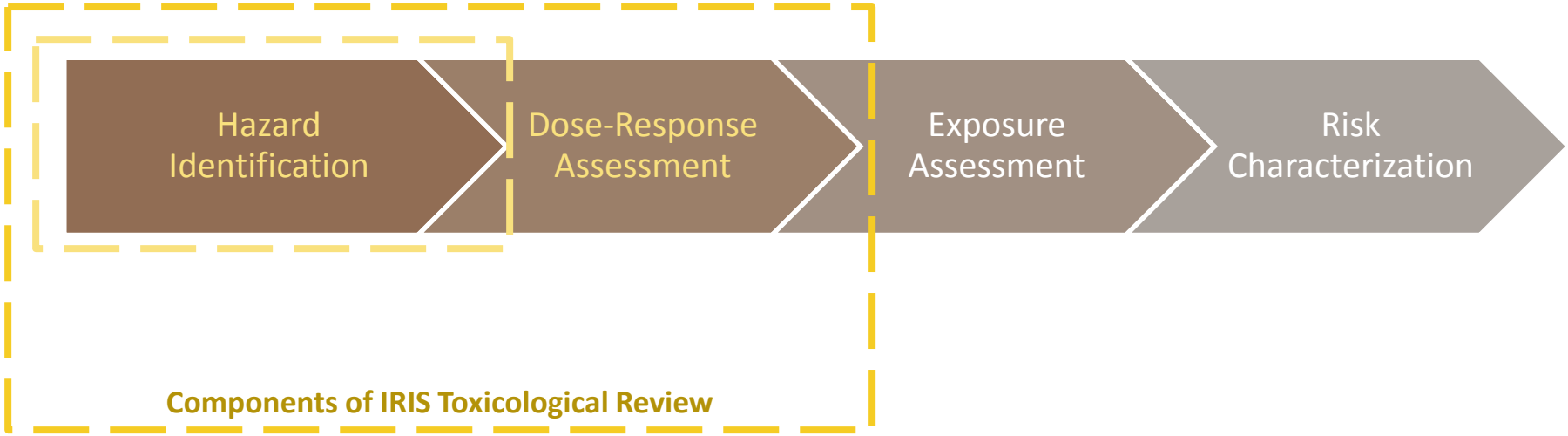
Hazard Identification in the Inorganic Arsenic Toxicological Review

- **Objective:** Characterize potential causal relationship between exposure to arsenic and health effects
  - Hazard identification **informs** dose response assessment



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Steps in Development of Hazard Identification

- Employ systematic approach to **identify evidence** and **evaluate evidence**
  - Ensures consistency and breadth
  - Approach described in previous presentation
- Expert judgment critical to **integrate evidence** and **assess causality**
  - No formula to reach appropriate conclusions
  - Goal is to answer the question:

Is arsenic exposure, measured before the development of ___[adverse health effect]___, associated with development of that adverse health effect?

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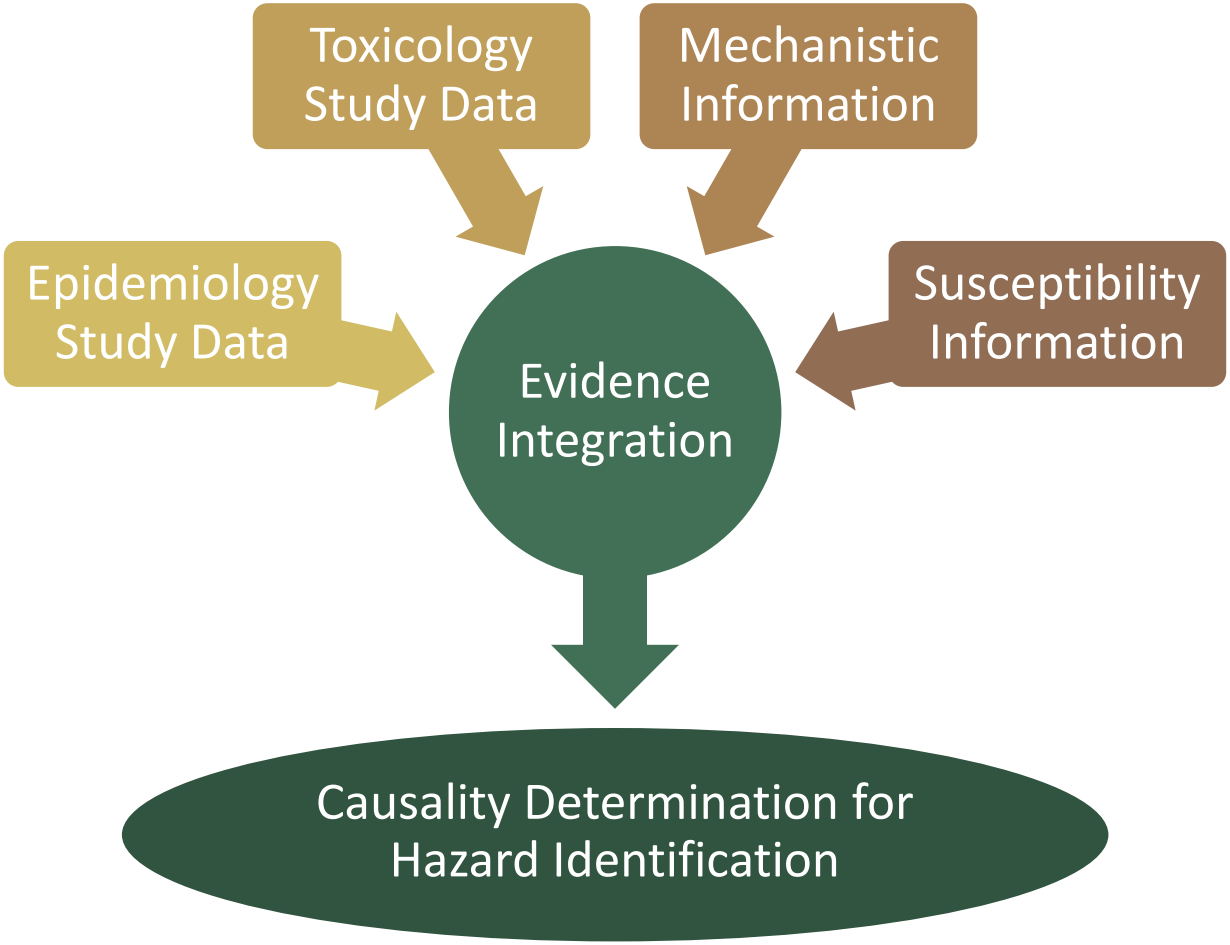
Data Supporting Hazard Identification



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Integrate Evidence from Epidemiologic Studies

- Development of hazard identification sections relies on:
  - **ROB results** to identify potential strengths and weaknesses of individual studies
  - **Evidence tables** which summarize data from individual studies
  - **Full-text publications** to provide study details not captured in evidence tables
  - **Expert judgment** to integrate all findings and draw appropriate conclusions

Above apply also to toxicology studies.

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Integrate Evidence from Animal Toxicology Studies

- Abundance of epidemiology data means less reliance on data from animal toxicology studies
  - Also, some shortcomings of toxicological data for arsenic
- Data from toxicology studies useful to
  - Provide supporting evidence for biological plausibility
  - Inform key questions remaining after review of epidemiologic data

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Integrate Evidence from Mechanistic Studies

- Develop qualitative summary to inform causal determination
- Mechanistic data can inform biologic plausibility
- For health effects determined to be “causal” and “likely causal,” comprehensive AOP analyses planned

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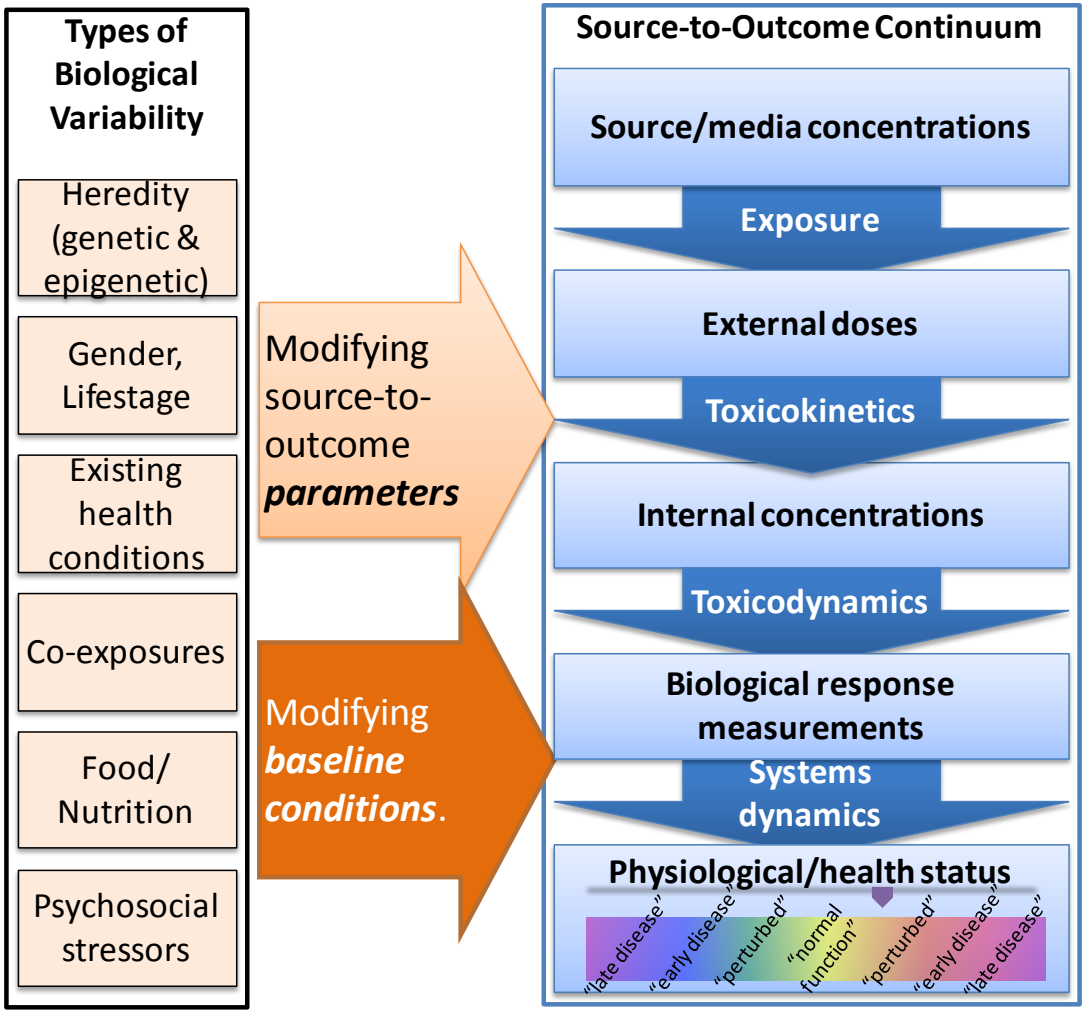
Integrate Evidence from Susceptibility Data

- Review references to categorize by health effect and response modifying factors
- Consideration of susceptible life stages and populations
  - Examine **susceptible groups** of the population
  - Evaluate whether **early life exposure** may affect risk of arsenic-related effects in adults
  - Essential to evaluate potential adverse effects on **fetal and postnatal exposure** to inorganic arsenic
- Evaluate response modifying factors using strength of evidence framework from EPA Integrated Science Assessments (ISA)

Potential Response Modifying Factors



Adapted from Zeise et al., 2013

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Strength of Evidence Framework for Susceptibility

Classification	Weight of Evidence for Health Effects
Adequate Evidence	Consistency within discipline Coherence across disciplines
Suggestive Evidence	Limited evidence Inconsistency within discipline Lack of coherence across disciplines
Inadequate Evidence	Insufficient quantity, quality, consistency, statistical power
Evidence of No Effect	Consistency within discipline Coherence across disciplines for No Effect

Adapted from EPA's Integrated Science Assessments

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Approach for Assessing Causality

- Evaluate potential causal relationship between inorganic arsenic exposure and health effect including evidence of:
  - Consistency
  - Strength of association
  - Biologic plausibility
  - Temporality
  - Biologic gradient
- Evidence integration narrative:
  - presents the conclusions from each line of evidence (i.e., human, animal, and mechanistic)
  - explains the reasoning that led to these conclusions
  - cites the studies that were pivotal to these conclusions
  - identifies the key issues and how they were resolved
  - integrates all lines of evidence to characterize the agent's association with each health outcome
- Evidence integration and assessment of causality require expert judgment

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Weight of Evidence for Causal Determination

Causal relationship	Rule out chance, confounding, and other biases Consistency, coherence, biological plausibility, high-quality studies
Likely to be a causal relationship	Multiple, high-quality studies show effects Some uncertainty remains overall
Suggestive but not sufficient to infer a causal relationship	Cannot rule out chance, confounding, other biases -Evidence is limited but supporting -Evidence is not entirely consistent
Inadequate to infer a causal relationship	Evidence is of insufficient quantity, quality, consistency
Not likely to be a causal relationship	Multiple studies consistently show no effect

Adapted from EPA's Integrated Science Assessments

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Hazard Identification Synthesis Summaries

- Summaries under development for each health effect
- Proposed section organization
  - Background
  - Database Overview
  - Summary of Evidence
  - Evidence Integration Table
  - Causal Determination

NRC Tier 1: Evidence of causal association

- Bladder cancer
- Lung cancer
- Ischemic heart disease
- Skin lesions
- Skin cancer

NRC Tier 2: Other priority outcomes

- Diabetes
- Immune effects
- Neurodevelopmental toxicity
- Nonmalignant respiratory disease
- Pregnancy outcomes (infant morbidity)
- Prostate cancer
- Renal cancer

NRC Tier 3: Other end points to consider

- Hypertension
- Liver cancer
- Pancreatic cancer
- Pregnancy outcomes (infant mortality)
- Renal disease
- Stroke

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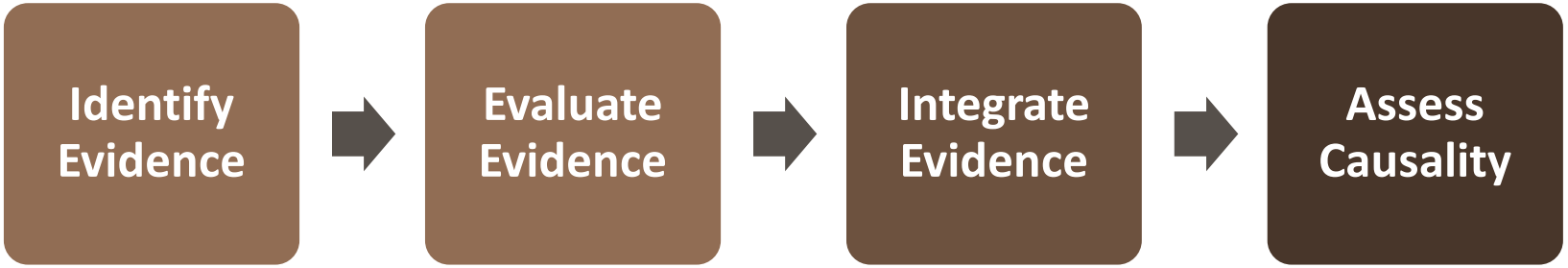
Summary: Hazard Identification

- Considers multiple streams of data (epidemiologic, animal toxicology, mechanistic, susceptibility) to answer question

Is arsenic exposure, measured before the development of __[adverse health effect]__, associated with development of that adverse health effect?



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Supplemental Information

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Strength of Evidence Framework for Susceptibility

Descriptor*	Strength of Evidence Considerations*
Adequate Evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or life stage being at increased risk of inorganic arsenic-related health effect(s) relative to some reference population or life stage. Where applicable this includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive Evidence	The collective evidence suggests that a factor results in a population or life stage being at increased risk of an inorganic arsenic-related health effect relative to some reference population or life stage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine if a factor results in a population or life stage being at increased risk of an inorganic arsenic-related health effect relative to some reference population or life stage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or life stage being at increased risk of inorganic arsenic-related health effect(s) relative to some reference population or life stage. Where applicable this includes coherence across disciplines. Evidence includes multiple high-quality studies.

Adapted from EPA's Integrated Science Assessments

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Weight of Evidence for Causal Determination

Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects; or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.
Suggestive but not sufficient to infer a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species; or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.

Adapted from EPA's Integrated Science Assessments