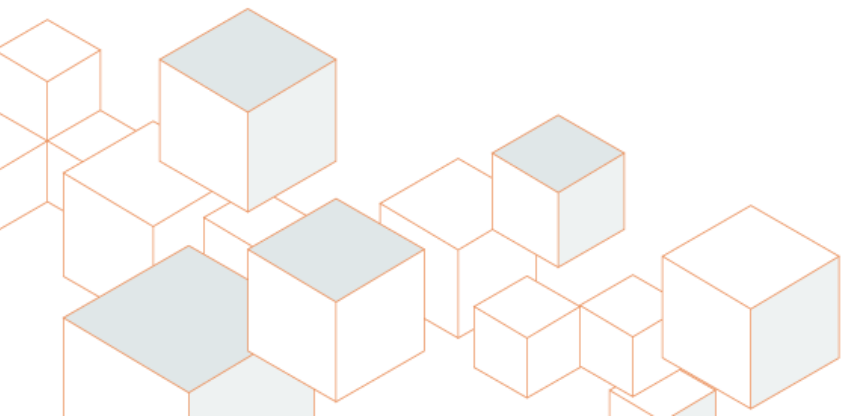# THE EPA BI-MONTHLY MEETING INORGANIC ARSENIC SCIENCE DISCUSSION

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SCIENCE ISSUE 1: APPLICATION OF NRC RECOMMENDATIONS

Strength of Evidence Framework for Susceptibility (Table 1-4)

Table 1-4   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 the Integrated Science Assessment for Lead (U.S. EPA, 2013)

Recommendation(s)

Need Clearer Descriptors

❑ "Suggestive" should be "above equipoise" or 'more likely than not'.

❑ Inconsistent studies should be treated as below equipoise (IOM 2008)

Institute of Medicine (IOM). 2008. Accessed at http://books.nap.edu/openbook.php?record_id=11908&, 781p.

Excerpt from Table 1-4, Page 1-29

The Causality Framework (Table 1-5)

Table 1-5 Causal Determination Framework

| Descriptor	Causal Determination Considerations
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding 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 are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes multiple high-quality studies.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. 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 that demonstrate effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example; (1) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or (2) a well-conducted toxicological study, such as those conducted in the National Toxicology Program (NTP), shows effects in animal species.
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 is suggestive of 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, are mutually consistent in not showing an effect at any level of exposure.

Excerpt from Table 1-5, Page 1-33

Recommendation(s)

- ❑ Framework should be for 'associations', not 'causation'
  - ➢ The RoB focuses on observed associations (Page 1-53)

- ❑ Should be based on totality of high quality and relevant evidence, not just one good study.

- ❑ When determining 'likely to be causal' must explore alternative hypotheses and their plausibility

- ❑ Need to define "reasonable confidence"

- ❑ Must consider actual exposure levels

The Conceptual Model (Figure 1-3)

Recommendations

(1) Dose-relevance should be incorporated

(2) Should not consider effects with 'no known MOA' as relevant to humans without considering the totality of evidence

(3) Total arsenic is not an appropriate metric for oral exposure if interested in effects of inorganic arsenic
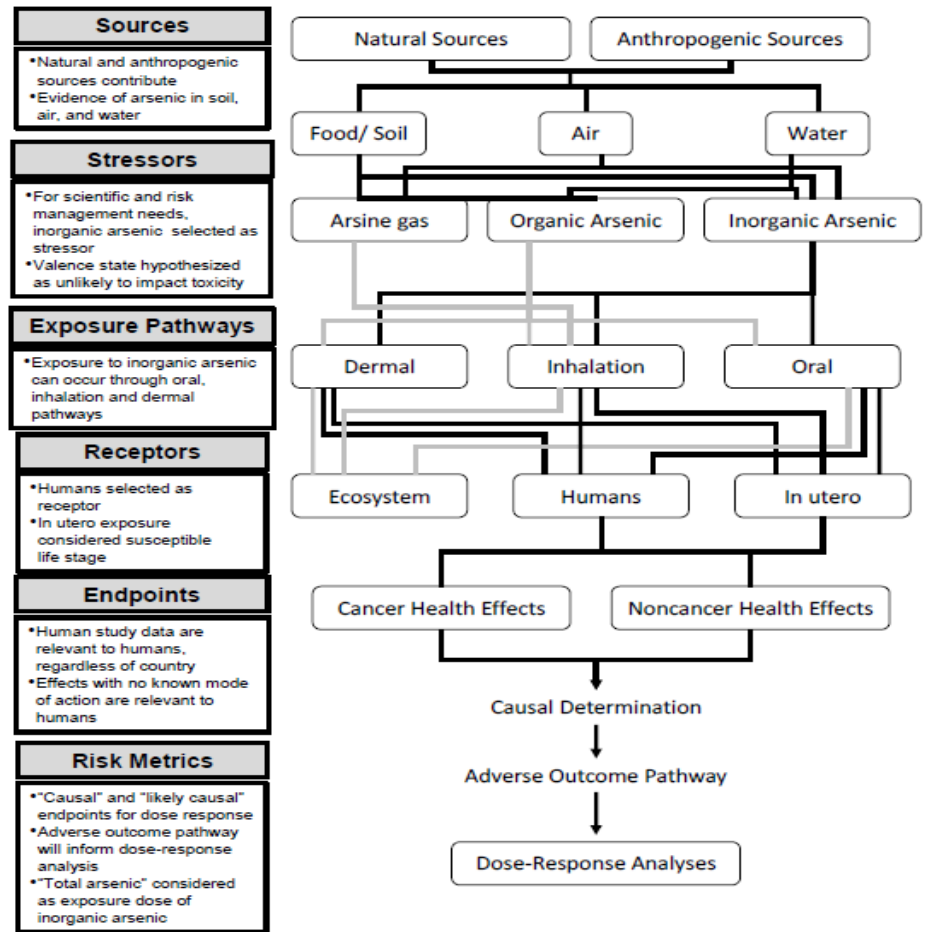
Figure 1-3   Overall Conceptual Model for Toxicological Review of Inorganic Arsenic

Excerpt from Figure 1-3, Page 1-39