

# Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic

## Why did the National Research Council do this study?

EPA has worked on updating its IRIS assessment of inorganic arsenic for many years. The agency faces the challenge of evaluating a large body of scientific information on inorganic arsenic, addressing recommendations for improving aspects of its past analyses of arsenic, and incorporating recommendations for generally improving hazard identification and dose-response analysis made in other National Research Council reports.

Congress mandated an independent review of the IRIS assessment of inorganic arsenic. In response, EPA requested that the National Research Council convene a committee to provide guidance during planning for the IRIS assessment, and then to review a draft of the assessment after the agency has considered the committee's recommendations and input from stakeholders.

In the first phase of the study—the focus of the present report—the committee offers recommendations on how EPA's IRIS assessment could address critical scientific issues in assessing the effects of oral exposure to inorganic arsenic. The committee's recommendations were informed by EPA's draft plans for performing the assessment, a workshop held to gather input on interpreting and applying scientific information on inorganic arsenic for hazard identification and dose-response analysis, and by the committee's preliminary survey of the scientific literature.

## What did the report find?

The report's findings and recommendations are focused in the key areas of hazard identification, systematic reviews, mode-of-action analyses, susceptibility, and dose-response analyses.

- **Hazard Identification:** Hazard identification is the process of identifying what health effects might be caused by an environmental agent. EPA's draft planning documents outline an improved approach to determining the cancer and noncancer effects that may be associated with exposure to inorganic arsenic. The approach involves screening the literature, evaluating studies, organizing the evidence, and using a causal determination framework to document how decisions are made about which health end points are linked to inorganic arsenic. Examples of evidence tables provided by EPA appear to capture the salient categories of information with respect to epidemiologic data. EPA's draft plans describe how a causal determination framework will be used to categorize evidence on different health end points into five possible categories. The committee supports this five-tier approach, and recommends that judgments are characterized with respect to standard criteria for causality. The assessment of causality will help EPA prioritize end points for subsequent analysis of mode of action and dose response.

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### ***What are EPA IRIS Assessments?***

The US Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) program develops toxicologic assessments of environmental contaminants. These assessments provide hazard identification and dose-response information. The information is then used in conjunction with exposure information to characterize risks to public health. Moreover, IRIS may be used in risk-based decision-making, in regulatory actions, and for other risk-management purposes.

### ***What is inorganic arsenic?***

Arsenic is a naturally occurring element in the environment. When combined with elements other than carbon, it is called *inorganic arsenic*. Inorganic arsenic is found in soil, groundwater, surface waters, air, and in some foods.

- **Systematic Reviews:** Systematic review is a method to comprehensively identify and evaluate the available scientific evidence using a transparent process. EPA has indicated that several systematic reviews of the scientific literature will be used to support its toxicologic assessment of inorganic arsenic. This work will help address questions raised during the hazard-identification process with respect to guiding the dose–response analysis. A statistical technique called meta-analysis could also be used as an evaluation tool to pool evidence from systematic reviews if certain conditions are met. The report provides guidance on how the agency should proceed with conducting systematic reviews and meta-analyses.
- **Mode-of-Action Analyses:** Analysis of mode-of-action involves characterizing the sequence of key events, starting with the interaction of inorganic arsenic with a cell, that lead to a certain health effect. EPA’s draft plans outline an evaluation process to organize mechanistic information to inform dose–response modeling with respect to the shape of the curve, particularly in the low dose region of the curve, and the understanding of human variability. The committee supports EPA’s plans to perform mode-of-action analyses for health outcomes on which there appears to be a causal or likely to be causal relationship with inorganic arsenic. The report provides further guidance on the approach such analyses could take.
- **Susceptibility:** Multiple factors can affect susceptibility to inorganic arsenic, including life stage, genetic factors, sex, nutritional deficiencies, health status, lifestyle (for example, smoking and alcohol

consumption), and coexposures. The committee agrees with EPA’s proposal to use probabilistic approaches in considering the uncertainty and variability associated with those factors. Although it is unclear that any susceptibility factors can be evaluated quantitatively in the assessment, their existence is an important consideration when evaluating population risk.

- **Dose–Response Analyses:** Epidemiologic data are expected to serve as the basis for the dose-response analyses performed for most health effects. EPA’s efforts should be directed at performing dose-response analyses in the range of epidemiologic observations. Should the data in the range of observation be inadequate for developing risk estimates that meet EPA’s needs, mode-of-action data should be used to the extent possible to extrapolate below the observed range. The committee concurs with EPA’s draft plan that even if a mode of action cannot be determined with reasonable certainty, dose-response analyses should be performed on health end points deemed to have a causal or likely causal relationship with arsenic. In the absence of mode-of-action data, alternative statistical approaches are recommended.

## Next Steps

After EPA completes its draft IRIS assessment of inorganic arsenic, the National Research Council committee will review the draft to determine whether the committee’s recommendations were appropriately addressed and whether the assessment also reflects recommendations for improving IRIS assessments made in prior National Research Council reports.

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The National Academies appointed the above committee of experts to address the specific task requested by the US Environmental Protection Agency. The members volunteered their time for this activity; their report is peer-reviewed and the final product signed off by both the committee members and the National Academies. This report brief was prepared by the National Research Council based on the committee’s report.



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