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Assessment Development Plan for the Integrated Risk Information System (IRIS) Toxicological Review of Inorganic Arsenic

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CONTENTS

TABLES

FIGURES

BOXES

PREFACE

For the Integrated Risk Information System (IRIS) Program, the National Center for Environmental Assessment (NCEA) at the U.S. Environmental Protection Agency (EPA) is developing a state-of-the-science *Toxicological Review of Inorganic Arsenic*. The approaches NCEA is applying to assess the hazard and dose-response of inorganic arsenic, and the associated uncertainty, are based on evolving practices in the IRIS Program and are guided by National Research Council recommendations (2014, 2013, 2011, 2009). Many of these approaches have yet to be used extensively in environmental health assessment. Inorganic arsenic provides an opportunity to explore these approaches because numerous human observational studies of environmental exposures are available. IRIS Toxicological Reviews are incorporating several new elements as part of this evolving process: comprehensive problem formulation and planning involving stakeholders, specific questions to guide risk-of-bias evaluations, and explicit quantitative consideration of sensitive subpopulation risks and risk modifiers. The reviews also integrate thorough analyses of adverse outcome pathways and networks to inform causal determinations and dose-response model choices, Bayesian regression meta-analyses of studies to examine dose-response, and Bayesian analyses of uncertainties. The results of these evaluations will enable EPA to refine these new approaches and consider their utility for application to other types of assessments. Of note is that the data required for many of these approaches are usually unavailable for most chemicals the IRIS Program evaluates. Moreover, these approaches might not be fit for purpose for other assessments. Consequently, the use of these approaches in developing the *Toxicological Review of Inorganic Arsenic* does not necessarily signal a change from current assessment approaches for other NCEA products.

EXECUTIVE SUMMARY

For the Integrated Risk Information System (IRIS) Program, the National Center for Environmental Assessment (NCEA) at the U.S. Environmental Protection Agency (EPA) is developing a state-of-the-science *Toxicological Review of Inorganic Arsenic*. This Assessment Development Plan presents an overview of the types of scientific information and technical approaches EPA will consider when developing the draft Toxicological Review. Additional supporting materials are available on the IRIS inorganic arsenic webpage.[1]

The scientific information considered and the approaches proposed were informed by the National Research Council's (NRC, 2013) Interim Report, *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic*,[2] and several other NRC reports NRC (2014); (2011, 2009). EPA Program and Regional Offices, other federal agencies, and public stakeholders have actively participated in the scoping and planning for the Toxicological Review and in the review of draft preliminary materials. Based on their recommendations, the Toxicological Review will examine the cancer and noncancer effects from oral, inhalation, and potentially dermal exposure to inorganic arsenic. Adverse outcome pathway and network analyses and susceptible populations also will be considered, as feasible.

The key messages in this Assessment Development Plan are:

- The IRIS Toxicological Review for arsenic will evaluate the efficacy of several NRC-recommended innovations. Based on these evaluations, approaches will be refined and their utility for broader application determined. Approaches ultimately used in the *Toxicological Review of Inorganic Arsenic* do not necessarily signal a change from current assessment approaches used for other NCEA products.
- This plan represents the fruition of an extensive problem formulation and planning effort with substantial NRC and stakeholder involvement.
- A formal, systematic review of the literature has been conducted, informed by the National Toxicology Program's (NTP) Office of Health Assessment and Translation approach. Results should not be interpreted as a checklist to exclude or include studies automatically, but rather as an investigation of one approach to literature evaluation.
- For hazard identification, the Toxicological Review will, as feasible:
  - Consider all endpoints identified by NRC (2013) in their Interim Report.
  - Identify susceptible subpopulations and risk modifiers.

[1] http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=278&forceAssessmentTab=true.
[2] http://www.nap.edu/catalog/18594/critical-aspects-of-epas-iris-assessment-of-inorganic-arsenic-interim.

- Develop adverse outcome pathway or network analyses for endpoints considered to be causally or likely causally associated with specific adverse outcomes, or having ambiguous causal determinations based on epidemiologic data only.
- Identify and present characteristics and results for all studies considered for hazard identification and dose-response in evidence tables.
- Base causal determination on integration of these data and expert judgment.

- For dose-response analyses, the following will be completed, as warranted and feasible:
  - Estimate noncancer and cancer risks for causal or likely causal endpoints, including risk-specific doses.
  - Consider non-U.S. and U.S. information on dietary contributions to total exposure and use available data and pharmacokinetic models to characterize urinary biomarkers of exposure compared to exposure.
  - Explicitly consider observational data at U.S. exposure levels down to background exposure (total urinary arsenic ~ 1–5 µg/L).
  - Evaluate susceptible subpopulations and risk modifiers (such as different phenotypes and smokers).
  - Apply various dose-response models and present the results.
  - Conduct meta-analyses of epidemiologic data.
  - Use adverse outcome pathway or network analyses, and human variability and susceptibility data, to inform extrapolations below the observed range of dose-response.
  - Possibly conduct additional adverse outcome pathway or network analyses for a subset of causal and likely causal endpoints for which dose-response models significantly diverge in the low-dose range.
  - Conduct Bayesian analyses to account for prior information and characterize uncertainties more fully (e.g., study selection, model choice).
  - Treat more complex analyses as limited in application (e.g., subset of endpoints) or as illustrative only, depending on outcomes.
- EPA will continue to take advantage of opportunities to engage Agency Program and Regional Offices, other federal agencies, the Executive Office of the President, and public stakeholders.

1. BACKGROUND

This section summarizes major activities completed since publication of the 1988 *IRIS Toxicological Review of Inorganic Arsenic*.

Box 1-1. History

- 1988: EPA published the *IRIS Health Hazard Assessment for Inorganic Arsenic*.
- 1999: The National Research Council (NRC), at EPA's request, published *Arsenic in Drinking Water*.
- 2003: EPA began updating the 1988 IRIS Toxicological Review.
- 2005: EPA released the draft *IRIS Toxicological Review of Inorganic Arsenic* for public comment and peer review.
- 2007: An expert panel convened by EPA's Science Advisory Board completed a review of key scientific issues included in the draft Toxicological Review and published comments in an advisory report.
- 2010: EPA released the revised draft *IRIS Toxicological Review of Inorganic Arsenic* for public comment and peer review.
- 2010: SAB completed its review of the draft Toxicological Review.
- 2011: Congress directed EPA to contract with the NRC to review the draft Toxicological Review.
- 2013 (January): EPA held a public scoping and problem formulation meeting for development of a new *IRIS Toxicological Review of Inorganic Arsenic*.
- 2013 (March–July): EPA held eight science issues public webinars.
- 2013 (May): EPA submitted a draft Assessment Development Plan and preliminary assessment materials to NRC for review.
- 2013 (November): NRC released the interim report, *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic* and provided recommendations; NRC supported EPA's plan.
- 2014 (June): EPA held a public science meeting to present and encourage comments on the Assessment Development Plan, preliminary assessment materials, and key science issues.

1.1. Previous EPA Assessments of Inorganic Arsenic and NRC Evaluations

EPA completed and published a final *IRIS Health Hazard Assessment for Inorganic Arsenic* in 1988 (see Box 1-1). In 1996, EPA asked NRC to evaluate the inorganic arsenic database and recommend revisions to the 1988 Health Hazard Assessment. In response, NRC published *Arsenic in Drinking Water* (NRC, 1999) and an update in 2001. In 2003, EPA began incorporating recommendations from the 1999 and 2001 NRC reports into a new, draft *IRIS Toxicological Review*

of Inorganic Arsenic. EPA also divided the Toxicological Review to focus on cancer outcomes and noncancer outcomes separately. In 2005, EPA released a draft *IRIS Toxicological Review of Inorganic Arsenic* of cancer health effects following oral exposure and requested comments from the public and review by EPA's Science Advisory Board (SAB). The SAB provided recommendations to EPA in 2007 (SAB, 2007), which EPA subsequently incorporated into the Toxicological Review. The revised draft IRIS Toxicological Review of cancer health effects following oral exposure to inorganic arsenic was released for public comment and SAB review in 2010 (U.S. EPA, 2010). The SAB provided their comments and recommendations the following year (SAB, 2011).

1.2. Congressional Directive for EPA Toxicological Review of Inorganic Arsenic

In December 2011, Congress directed EPA (U.S. Congress, 2011) to contract with NRC to review EPA's draft inorganic arsenic Toxicological Review. Congress asked NRC to conduct a two-phase review of the Toxicological Review, considering both cancer and noncancer hazards from oral exposure to inorganic arsenic. For the first phase, NRC was directed to review the scope and key science issues and provide recommendations to EPA for developing a draft Toxicological Review. For the second phase, NRC was directed to provide EPA with a critical scientific peer review of the draft.

1.3. The NRC Interim Report, *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic*

NRC conducted the first phase of its review between July 2012 and November 2013. A special committee convened by the NRC collected and reviewed information on hazard identification and dose-response analysis of inorganic arsenic during an NRC-sponsored workshop in April 2013.[3] The committee evaluated and commented on draft materials that EPA provided related to the ongoing IRIS Toxicological Review, including planning and scoping documents, reports from workshops EPA conducted, and a draft plan for completion. That draft plan, a predecessor to this Assessment Development Plan, described EPA's proposed technical approaches for literature searches and evaluation, hazard identification, and dose-response and uncertainty analyses. NRC presented the results of the first phase of its review in the 2013 Interim Report, *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic* (NRC, 2013). The report comments on key aspects of inorganic arsenic toxicology and provides specific recommendations to EPA for conducting the IRIS Toxicological Review.

The NRC stated that the scoping materials submitted for review clearly demonstrated that EPA is incorporating previous NRC recommendations (NRC, 2011, 2009) to involve risk managers, risk assessors, and stakeholders early in the development process. Regarding EPA's analysis plans,

[3] http://www2.epa.gov/iris/inorganic-arsenic-workshop.

NRC observed that the draft approach for searching and evaluating the literature likely would capture the salient information from epidemiologic studies but suggested that collecting animal and in vitro data also could be important for adverse outcome pathway and network (AOP/N) analyses.[4] NRC acknowledged that the outlined approaches to incorporate systematic review in EPA's plan also reflect NRC recommendations (NRC, 2011, 2009).

For hazard identification, EPA proposed evaluating the relationship between inorganic arsenic exposure and human health effects using a causal determination framework as previously described (U.S. EPA, 2013a, c, 2005). NRC supported this approach as well as the proposal to consider animal and mechanistic data as supporting evidence for determining causality. NRC prioritized specific health endpoints to evaluate for hazard identification (see Box 1-2) and stated that EPA will refine these categorizations after it conducts a more comprehensive analysis. They also supported EPA's use of evidence tables to present information and stressed the importance of explaining causal determination judgments in the synthesis text. NRC supported EPA's proposal to perform AOP/N analyses on health endpoints considered "causal" or "likely causal." They recommended considering "suggestive" endpoints for AOP/N development to inform causal determination. The committee agreed with EPA's proposal to conduct dose-response analysis for "causal" or "likely causal" relationships even if an AOP/N cannot be determined. The AOP/N process "will be used to organize mechanistic information to determine how mechanistic information supports low-dose extrapolation and to inform how dose-response analyses account for the

Box 1-2. Hierarchy of Health Endpoints of Concern for Inorganic Arsenic

Tier 1: Evidence of a causal association determined by other agencies or in published systematic reviews

- Lung, skin, and bladder cancer
- Ischemic heart disease
- Skin lesions

Tier 2: Other priority outcomes

- Prostate and renal cancer
- Diabetes
- Nonmalignant respiratory disease
- Pregnancy outcomes
- Neurodevelopmental toxicity
- Immune effects

Tier 3: Other endpoints

- Liver and pancreatic cancer
- Renal disease
- Hypertension
- Stroke
- Pregnancy outcomes (fetal loss, stillbirth, and neonatal mortality)

(Reproduced from NRC 2013)

[4] The NRC and stakeholders use the terms "adverse outcome pathway" and "mode of action" to describe conceptual models of underlying mechanisms of adverse health outcome. While the terms are similar, adverse outcome pathway models are adverse outcome specific rather than chemical specific (but can be informed by chemical-specific information), whereas, mode of action models are generally chemical specific. EPA and other Organization for Economic Co-operation and Development members are moving toward use of adverse outcome pathways or networks to describe mechanistic conceptual models; hence, the terms adverse outcome pathway or networks are used throughout this document unless quoting another source where mode of action is used. Specifically, an AOP is defined as a "conceptual framework that organizes existing knowledge concerning biologically plausible, and empirically supported, links between molecular-level perturbation of a biological system and an adverse outcome at a level of biological organization of regulatory relevance" (Villeneuve et al., 2015). Multiple, interconnected AOPs related to the same disease, and which more broadly capture underlying events, are termed adverse outcome networks (AONs).

uncertainty associated with susceptibility" (NRC, 2013). Applications of AOP/N analyses are discussed in Section 3.

NRC made several recommendations for the dose-response analysis. They stated that EPA should develop risk estimates across the array of health effects having adequate epidemiologic evidence. They recommended performing the analyses with data in the range of epidemiologic observations. When those data are not available, they recommended using AOP/N analyses to inform dose-response model choices when extrapolating below the range of observed data. They cautioned, however, that extrapolations become increasingly uncertain the farther below the observed range they are made. They also stated (1) extrapolations should be limited to within an order of magnitude; and (2) although they do not assume that background concentrations are with or without health effects, assessing health risk could be facilitated by characterizing dose-response relationships down to background concentrations. NRC recommended that EPA derive risk-specific doses, which would facilitate subsequent efforts to evaluate cumulative risk, conduct risk-benefit evaluations, and perform comparative analyses.

NRC agreed with EPA's proposal to use probabilistic approaches when considering variability and uncertainty associated with susceptibility factors. Susceptibility due to preexisting disease, early-life exposure, and sex differences in metabolism were among several factors NRC recommended for consideration. Based on available evidence, the committee suggested considering whether dose-response analyses should focus on the population as a whole or involve separate approaches for the general population and susceptible groups.

1.4. June 2014 IRIS Public Science Meeting on Inorganic Arsenic

Following the publication of the NRC (2013) interim report, EPA compiled preliminary materials for the *IRIS Toxicological Review of Inorganic Arsenic* for public review. Materials included an updated Toxicological Review Development Plan, a description of the literature search strategy and systematic review methods, summaries of relevant epidemiologic and animal toxicity studies identified to date and key evidence from those studies, and information on AOP/N and susceptibility. EPA solicited public input on these preliminary materials, and comments received are available in the inorganic arsenic docket (EPA-HQ-ORD-2012-0830[5]). EPA also invited the public to make presentations on key science issues at a public science meeting[6] held June 2014.

[5] http://www. regulations.gov/#!searchResults;rpp=25;po=0;s=EPA-HQ-ORD-2012-0830;fp=true;ns=true.
[6] http://www2.epa.gov/iris/iris-bimonthly-public-meeting-jun-2014.

2. KEY CHARACTERISTICS OF THE ASSESSMENT

This section describes overall objectives and features of this Assessment Development Plan.

Box 2-1. Key Messages

- The goal for the Assessment Development Plan is to highlight the fundamental considerations and potential approaches for the *IRIS Toxicological Review of Inorganic Arsenic*, communicate these topics, and facilitate discussion on them.
- EPA will continue to seek and take advantage of opportunities to engage Agency Program and Regional Offices, other federal agencies, the Executive Office of the President, and public stakeholders in the discussions of the Toxicological Review.
- This Assessment Development Plan and additional supporting materials are available on the IRIS arsenic webpage to facilitate transparent understanding of the data and methods to be used.
- Included in this Assessment Development Plan is an analysis plan for hazard identification and dose-response assessment.

2.1. Goals of the Assessment Development Plan

The goals for the Assessment Development Plan are to highlight the basic considerations and potential approaches to be used in the *IRIS Toxicological Review of Inorganic Arsenic*, communicate EPA's intentions regarding these to stakeholders, and facilitate discussion on these topics. The Assessment Development Plan reflects the problem formulation and planning efforts EPA has completed to date. This plan and other materials are available on the IRIS inorganic arsenic webpage.[7]

2.2. Agency Partners and Public Stakeholder Engagement

EPA is committed to engaging EPA Program and Regional Offices, other federal agencies, the Executive Office of the President, and public stakeholders throughout the development of this Toxicological Review. Agency partners and public stakeholders (e.g., nongovernmental organizations, industry groups, citizens, academia) have been active participants in planning and scoping meetings, identifying their needs for the *IRIS Toxicological Review of Inorganic Arsenic*, and making scientific recommendations. Of note is that the *IRIS Toxicological Review for Inorganic*

[7] http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=278&forceAssessmentTab=true.

Arsenic is coordinated with ongoing assessments of food-related risks conducted by the U.S. Food and Drug Administration.

2.3. Transparency

EPA is committed to making certain the Toxicological Review proceeds transparently. Preliminary materials being used to develop the Toxicological Review are available to the public on the IRIS inorganic arsenic webpage[8] and the HERO project page for inorganic arsenic.[9]

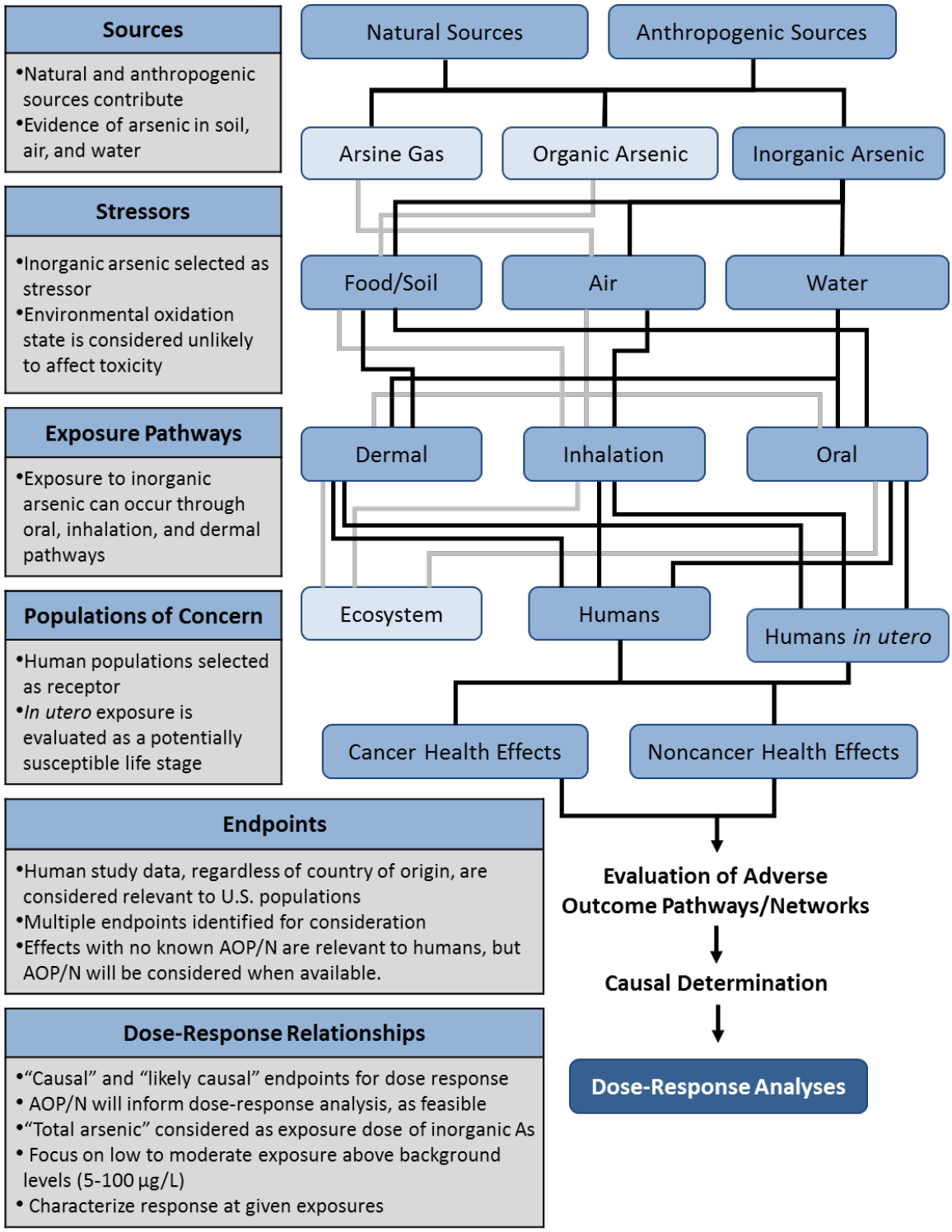
2.4. Timeline for Completion

The comments received at the June 2014 IRIS Public Science Meeting and the plan described here inform the development of the draft Toxicological Review. The draft Toxicological Review will undergo internal EPA review, review by other federal agencies, and the Executive Office of the President. It will be made publicly available for comment before it is released for external peer review, which NRC will perform. Following revisions and additional review by EPA, other federal Agencies, and the Executive Office of the President, EPA anticipates posting the final *IRIS Toxicological Review of Inorganic Arsenic* to the IRIS database in 2017.

2.5. Overall Conceptual Model

The conceptual model EPA has developed for the Toxicological Review is illustrated in Figure 2-1. In Figure 2-1, black lines and darker blue boxes indicate relationships and elements that EPA will consider in the Toxicological Review; gray lines and lighter blue boxes indicate aspects of inorganic arsenic exposure that are outside the scope of this Toxicological Review. Additional discussion of the conceptual model is found in *Draft Development Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Inorganic Arsenic* on the IRIS website.[10]

[8] http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=278&forceAssessmentTab=true.
[9] http://hero.epa.gov/index.cfm/project/page/project_id/2211.
[10] http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=524796#_ga=1.136360240.1891222957.1444405714.



Source: Adapted from NRC (2009).

Figure 2-1. Overall conceptual model for *IRIS Toxicological Review of Inorganic Arsenic*.

3. ANALYSIS PLAN FOR THE TOXICOLOGICAL

This section describes the analysis plan. Figure 3-1 illustrates the technical activities as a series of generally sequential steps.

Box 3-1. Key Messages

- The analysis plan describes how the Toxicological Review will be implemented.
- A systematic literature search and review process identifies and selects studies, evaluates study methods based on clearly defined criteria, and transparently documents the selection outcome.
- The analysis plan and additional material on the Web describe approaches to hazard identification and dose-response analysis, including systematic review, adverse outcome pathway or network analyses, and uncertainty analyses.
- The analysis plan is flexible and can be modified as the Toxicological Review is developed, depending on data and analytical requirements.
- This plan has been revised in response to NRC recommendations in the interim report *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic* (NRC, 2013); public input from the June 2014 IRIS Public Science Meeting on Inorganic Arsenic; and recommendations in the NRC report, *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC, 2014).

3.1. Literature Search

This section describes the approach used for identifying relevant literature and evaluating risk of bias. EPA systematically reviewed and evaluated the available literature on inorganic arsenic to guide expert judgment, as NRC recommended in its report, *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC, 2014). The review process formulates specific strategies to identify and select studies, evaluates methods used in the studies based on clearly defined criteria, and transparently documents the process and its outcomes.

Literature Identification

The initial literature search process for the Toxicological Review included selecting databases of references, defining search terms, documenting search strategies, and selecting a stopping date for literature searches. EPA conducted searches using the HERO interface, updated through July 2014. The resulting literature search products are publicly available on the HERO

project page for inorganic arsenic.[11] The outcome of the literature search process was a comprehensive list of the available scientific literature on inorganic arsenic.

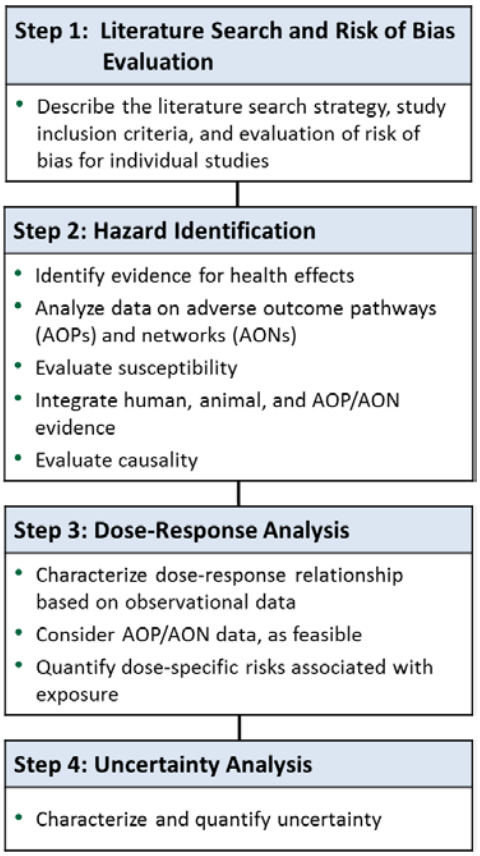


Figure 3-1. Overview of the analysis plan for *IRIS Toxicological Review of Inorganic Arsenic*.

Figure 3-2 outlines the literature search strategy for information on health effects and mechanistic data for the *IRIS Toxicological Review of Inorganic Arsenic*. PubMed, Web of Science, and TOXLINE were searched using the chemical name and CAS (Chemical Abstracts Service) number. The results from the three databases were combined, and duplicate records were removed. The gray lines in Figure 3-2 indicate literature set aside during the literature search process; the dark lines indicate the progression of literature being considered during development of the Toxicological Review. Although not explicitly depicted in this figure, pharmacokinetic information is also captured in the "Mechanistic Data Cluster."

Non-peer-reviewed articles, abstracts, posters, and review articles were separated in the initial screening of the comprehensive list of references. The Agency uses only peer-reviewed articles in IRIS Toxicological Reviews. Posters are often not publicly available or peer reviewed, and although abstracts and review articles were considered potential sources for identifying additional

[11] http://hero.epa.gov/index.cfm/project/page/project_id/2211.

peer-reviewed references, the Toxicological Review relies on data from primary source material. As shown in Figure 3-2, the remaining references in the considered list were grouped using natural language processing. A computer algorithm was initially used to group references into "clusters" based on text similarities in the titles and abstracts. The clustering process is a tool to organize the arsenic literature database.

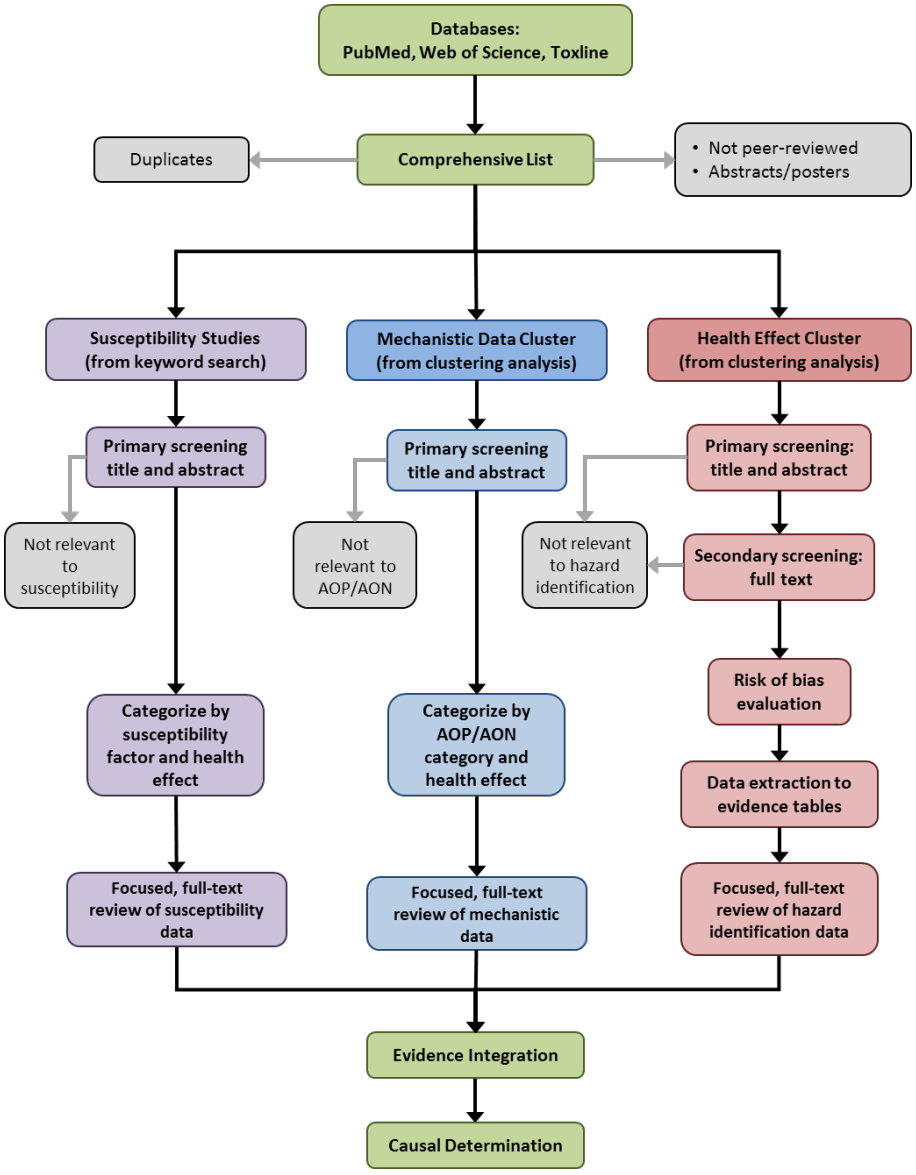


Figure 3-2. Process for identifying, sorting, and evaluating susceptibility, mechanistic, and health effect studies for the *IRIS Toxicological Review of Inorganic Arsenic*. Studies reporting health effect data often also include susceptibility and mechanistic data; targeted searches or cluster analyses enable identification of these data to support planned susceptibility factor evaluations and AOP/N analyses. (Colors depict data streams for each type of literature searched.)

Following the screening by title and abstract, the full text of all epidemiologic and toxicology studies identified was further reviewed to identify characteristics of the study design and the health effects reported in the study to determine if the study would inform the hazard identification for inorganic arsenic. All screening process results are captured in the publicly available HERO project page for inorganic arsenic.[12]

Risk-of-Bias Analysis

Epidemiologic and toxicology studies considered relevant for hazard identification were subject to risk-of-bias evaluations. Risk-of-bias evaluations assess some aspects of internal validity of study findings based on study design, conduct, and reporting. Risk-of-bias evaluations identify potential issues associated with chance, bias, or confounding so these can be considered in hazard identification (see Section 3.2). The risk-of-bias evaluation should not be considered a checklist or inclusion/exclusion criteria but rather a way to characterize potential strengths and weaknesses of individual studies more transparently. Risk of bias for each study was evaluated using the questions and considerations proposed in the Office of Health Assessment and Translation (OHAT) approach (NTP, 2013). The OHAT approach was developed initially from clinical and animal toxicology experience and has not previously been extensively evaluated using epidemiologic studies. Application to the arsenic database helps evaluate the approach's efficacy for application to epidemiologic data. The OHAT approach will not necessarily be applied for other IRIS Toxicological Reviews, nor does this change necessarily signal a departure from current assessment approaches used for other NCEA products. Note that each study was evaluated in isolation; if clarification of a risk-of-bias issue is reported in another paper, this was not considered.

Individual studies were evaluated using series of questions regarding potential sources of bias (Table 3-1). Risk of bias was assessed for each study question using a four-point scale developed by OHAT that includes ratings of definitely low bias, probably low bias, probably high bias, and definitely high bias (Table 3-2). The supporting rationale for each rating applied was documented by the reviewer. In cases where the rationale for one of the bias domains might differ for different health effects presented in one study, those differences were noted. Risk-of-bias evaluations necessarily require subjective conclusions by an expert scientist. Each study was evaluated independently by two scientists who referred to the draft OHAT approach for systematic review (NTP, 2013) and arsenic-specific clarifications developed for each question. After independently reviewing a study, the two reviewers discussed differences and resolved any discrepancies between their ratings and rationales. The same risk-of-bias questions were applied across all epidemiologic studies or animal toxicology studies using different rating guidelines and arsenic-specific clarifications for each discipline. The OHAT approach does not produce an "overall" risk-of-bias rating for each study, and no overall risk-of-bias ratings or other descriptors were developed for the arsenic studies at the study level.

[12] http://hero.epa.gov/index.cfm/project/page/project_id/2211.

Table 3-1. Example risk-of-bias considerations

Category	Risk-of-bias questions[1]
Selection	1. Was administered dose or exposure level adequately randomized?
	2. Was allocation to study groups adequately concealed?
	3. Were the comparison groups appropriate?
	4. Did the study design or analysis account for important confounding and modifying variables?
	5. Did researchers adjust or control for other exposures that are anticipated to bias results?
Performance	6. Were experimental conditions identical across study groups?
	7. Did researchers adhere to the study protocol?
	8. Were the research personnel and human subjects blinded to the study group during the study?
Attrition	9. Were outcome data complete without attrition or exclusion from analysis?
Detection	10. Were the outcome assessors blinded to study group or exposure level?
	11. Were confounding variables assessed consistently across groups using valid and reliable measures?
	12. Can we be confident in the exposure characterization?
	13. Can we be confident in the outcome assessment?
Selective reporting bias	14. Were all measured outcomes reported?
Other	15. Were there no potential threats to internal validity (e.g., statistical methods were appropriate)?

[1] In consultation with OHAT, the wording of Questions 7, 9, and 15 included in the 2013 draft (NTP, 2013) was changed so that answering "yes" would consistently indicate lower risk of bias, while answering "no" would indicate higher risk of bias.

Table 3-2. General risk-of-bias ratings

Rating	Description
(++) Definitely low risk of bias	There is direct evidence of low risk-of-bias practices (direct evidence is an explicit statement(s), generally in the study report or through contacting the authors).
(+) Probably low risk of bias	There is indirect evidence of low risk-of-bias practices **OR** it is deemed by the risk-of-bias evaluator that deviations from low risk-of-bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias (indirect evidence provides information to address the risk-of-bias question but falls short of direct evidence).
(-) Probably high risk of bias	There is indirect evidence of high risk-of-bias practices **OR** there is insufficient information provided about relevant risk-of-bias practices.
(- -) Definitely high risk of bias	There is direct evidence of high risk-of-bias practices (could include specific examples of relevant high risk-of-bias practices).

Evidence Tables

All studies identified as potentially relevant for a specific endpoint, including key studies upon which hazard identification conclusions might be based and additional studies that might be used as supporting evidence as warranted, were included in the evidence tables. The hazard identification sections for each health outcome will further discuss strengths and weaknesses of studies included in the evidence tables. Evidence tables include information for comparing key features such as study design, exposure metrics, and dose-response information. In addition, EPA has searched for and specifically identified studies that partially or fully meet the following criteria NRC recommended: individual measures of arsenic exposure, measurements of arsenic that precede outcome, and low-to-moderate exposure to inorganic arsenic (≤100 µg/L drinking water). These latter studies will be specifically considered in the dose-response analysis, with the aim of better informing responses at lower doses. Although the studies that meet these criteria will be specifically evaluated, neither the hazard identification nor the dose-response analyses will be restricted to only studies meeting these criteria. This comprehensive approach is judged the best method for evaluating the full set of data available for this Toxicological Review. Adopting this approach does not necessarily signal a departure from current assessment approaches for other NCEA products.

3.2. Health Hazard Identification

For the hazard identification process for inorganic arsenic, the relevant evidence of health effects identified through the literature search will be summarized and then integrated as described in the Cancer Guidelines (U.S. EPA, 2005) and the Integrated Science Assessments for lead and ozone (U.S. EPA, 2013a, b), as supported by NRC (2013). These documents describe the Agency's process for integrating evidence and making judgments about causality for both cancer and noncancer endpoints. The process is depicted in Figure 3-3 and described in more detail in the following sections. Application of the Integrated Science Assessment framework for assessing causality to noncancer examinations within the IRIS Program is currently unique to arsenic.

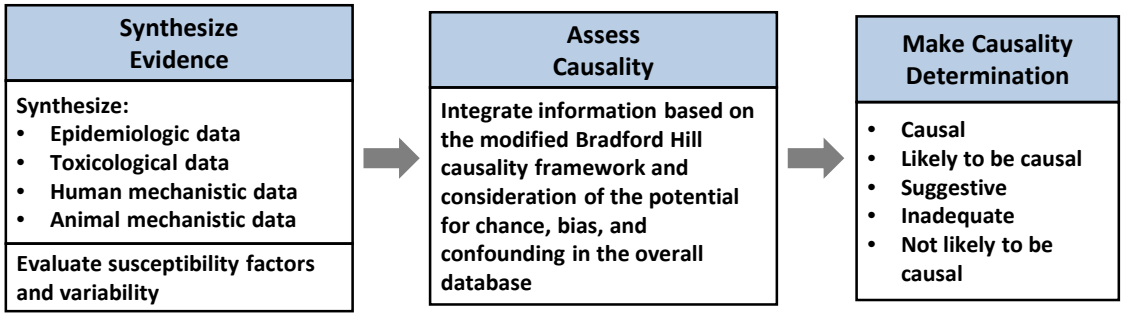


Figure 3-3. Overview of hazard identification for arsenic.

Evidence Synthesis

Epidemiologic studies, animal toxicology studies, and mechanistic studies can all inform the evaluation of health effects associated with inorganic arsenic exposure. These studies will be synthesized in hazard identification sections. These sections are not intended to provide detailed summaries of individual studies but rather to highlight the most informative evidence for considering causality. Hazard identification for inorganic arsenic will focus on studies conducted using relevant pollutant exposures. As NRC (2014) recommended, evidence will be integrated using expert judgment informed by the results of the risk-of-bias evaluations. Mechanistic data could provide additional information pertaining to causal determinations, human relevance of animal data, and insights into model choices for low-exposure extrapolation in the absence of observational data in the range of U.S. exposure levels. (Relevance to dose-response characterization is discussed below.) Evidence for susceptibility and population variability in responses also will be ascertained. Finally, the health effect synthesis sections will describe strengths and weaknesses in the available database and data gaps that limit the utility of the available data to inform hazard identification. Adverse health effects under consideration are shown in Box 3-2. Other effects identified in the hazard identification process will also be considered.

Box 3-2. Adverse Health Effects under Consideration

- Lung, skin, bladder, prostate, renal, liver, and pancreatic cancer
- Cardiovascular disease
- Skin lesions
- Diabetes
- Nonmalignant respiratory disease
- Pregnancy outcomes
- Neurodevelopmental toxicity
- Immune effects
- Renal disease

Evaluate Adverse Outcome Pathway or Network Data for Hazard Identification

As NRC (2013) noted, mode of action analyses "permit the integration of data to advance understanding of the coherence, biological plausibility, and human relevance of findings throughout the exposure-response continuum, and provide a transparent means of synthesizing the data." As part of the evidence synthesis for hazard identification, EPA will collect and analyze AOP/N information for each health endpoint of significant concern. For this Toxicological Review, EPA plans to consider both disease- and chemical-specific information in building conceptual models of mechanisms and link initial molecular-initiating events to population-level responses, as feasible. In addition to influencing hazard identification, AOP/N analyses might inform the shape of the dose-response curve beyond the range of the observational data. (See the description of dose-response model selection in Section 3.3 for more discussion.) The analyses also could be used to inform susceptibility and variability features, integrate mechanistically related outcomes, and help evaluate multiple risk modifiers (e.g., preexisting disease backgrounds, differences in genetic susceptibilities, smoking, alcohol consumption, diet). EPA plans to follow the NRC-recommended steps for mechanistic analyses and the Organization for Economic Co-operation and Development guidance on AOP development (OECD, 2013), to the extent feasible; however, early analyses

suggest that data might not be available to execute the NRC vision fully. Tables and diagrams will be created in the AOP/N analysis section to summarize the available information considered during evaluation of underlying mechanisms for adverse effects.

Evaluate Susceptibility Factors

Several factors could modify the association between exposure to inorganic arsenic and health outcomes among potentially susceptible populations. To identify susceptibility factors, the synthesis sections on health effects will evaluate the available evidence on factors such as life stage and early-life exposures, intrinsic variability (e.g., genetic makeup), and influence of environmental factors using an evidence-of-susceptibility framework (see Chapter 5 in U.S. EPA (2013a) for additional discussion). The evaluation process will focus on studies identified through a literature search within the overall arsenic literature database. The susceptibility analysis will focus primarily on human susceptibility, and to a lesser extent on animal susceptibility. Similarly, mechanistic data might be used to inform the observations from human and animal data.

The evaluation of susceptibility factors will focus primarily on studies with stratified analyses (i.e., epidemiologic) that compare populations or life stages exposed to similar inorganic arsenic concentrations within the same study design. Animal toxicology studies also might provide evidence of susceptibility factors that influence human responses to inorganic arsenic exposure as observed in epidemiologic studies. For instance, animal studies that examine developmental outcomes or use animal models with genetic polymorphisms can aid in understanding how life stage or the presence of genetic polymorphisms affect response. These data, in turn, support assertions of coherence between toxicologic and epidemiologic findings and the biological plausibility of the health effect. The results will be used to determine whether a particular factor alters the occurrence of effects from inorganic arsenic exposure and to inform the exposure-outcome relationship, as feasible. Tables will be created to summarize the available information considered during evaluation of potential populations of concern for the *IRIS Toxicological Review of Inorganic Arsenic*.

Evidence Integration and Causal Determinations

The process of evidence integration and causal determinations will be based on information presented in the hazard identification synthesis (see Figure 3-3). Appendix A of this document provides more discussion, and additional information on the process of evidence integration is provided in the draft development materials for this Toxicological Review (U.S. EPA, 2014) and EPA's guidelines for carcinogen risk assessment (U.S. EPA, 2005). Aspects of an association that suggest causality are drawn from Hill (1965), elaborated by Rothman and Greenland (1998), and referenced in other risk assessment documents (HHS, 2014; U.S. EPA, 2013a; IOM, 2008; IARC, 2006; U.S. EPA, 2005; HHS, 2004). Additionally, recommendations from the NRC review (NRC, 2014) influence this process.

3.3. Dose-response Analyses

Dose-response analyses will be developed for cancer and noncancer health endpoints for which inorganic arsenic exposure is "causal" or "likely causal." Consistent with NRC (2013) recommendations, one focus of the dose-response analyses will be epidemiologic observations for exposures ranging from background levels in drinking water to 100 µg/L in drinking water, which would encompass exposures commonly found in the United States. (Background levels of exposure would result in concentrations of 1–5 µg/L or less in urine, summing inorganic, monomethyl, and dimethyl arsenic forms.) Other, higher exposure levels also will be considered informative. As noted above, AOP/N information will be evaluated for the potential to inform dose-response analyses for endpoints that have inadequate epidemiologic data for characterizing dose-response at lower exposures. Additionally, AOP/N analyses could help characterize human variability and susceptibility. Variability and uncertainty will be characterized, including variability and uncertainty within and across models (and associated with model choices), among studies, and between individuals.

Where appropriate, EPA will consider approaches for evaluating changes in continuous effects (e.g., impact on IQ or blood pressure) in addition to dichotomous endpoints (binary outcomes, such as whether cancer has occurred). Possible approaches include assessing potential changes in distributions compared to background distributions and estimating changes in incidence above clinical or other thresholds (e.g., changes in blood pressure that lead to hypertension).

Outputs for cancer and noncancer evaluations will be equations describing the dose-response relationships. Accompanying these equations will be tables and plots that express risks associated with various exposures (e.g., in ppm), doses (e.g., in mg/kg-day), or biomarker (e.g., urinary) levels of inorganic arsenic (e.g., exposures, doses, or concentrations associated with estimated lifetime cancer risk of 1 in one million, 1 in one hundred thousand, 1 in ten thousand). These risks will be presented with confidence bounds that account for identified sources of variability and uncertainty to the extent the data can support such analyses.

Data Selection for Dose-response Analyses

For inorganic arsenic, dose-response analyses will be performed for health effects for which inorganic arsenic is determined "causal" or "likely causal." These analyses likely will be performed using epidemiologic data.

Meta-analyses that use data from multiple studies will be performed if at least three studies are available having exposures corresponding to intakes of drinking water with inorganic arsenic concentrations less than or equal to 100 µg/L (or comparable equivalent) and exposure metrics that are suitable for combined analyses. In addition, other studies that do not meet these criteria but contribute to our understanding of potential health effects and exposure-response relationships will be analyzed, including data with "sufficient" or "adequate" evidence of susceptibility. These dose-response analyses will inform the potential dose-response differences in susceptible

populations. Other factors influencing selection of studies for dose-response analyses of individual studies and meta-analyses include elements that potentially bias study results (e.g., methods of endpoint evaluation, controlling for confounders, studies with and without individual data, exposure misclassification).

Although an exposure assessment is beyond the scope of the Toxicological Review, aspects of exposure characterization are relevant to the use of such data in dose-response analyses. For estimating total daily exposure, NRC indicated that delineation of exposure sources (i.e., drinking water, diet, air) should be characterized, preferably using probabilistic approaches (NRC, 2013). In response to this recommendation, EPA will qualitatively and, where possible, quantitatively delineate between sources of exposure and consider information provided by biomarkers of exposure. Studies conducted on U.S. populations and other populations (e.g., Taiwanese, Bangladeshi) will be evaluated for hazard identification and a determination made on whether an adjustment in estimated dose-response behavior in the U.S. population is warranted.

A critical aspect of exposure pathway considerations is capability to estimate intake or internal dose, or both, based on available data. EPA will evaluate the feasibility for qualitative and quantitative analyses based on the available data and physiologically based pharmacokinetic model(s).

EPA also will consider exposure uncertainty in collecting data for dose-response analyses. For example, studies might report arsenic concentrations for a particular route of exposure (e.g., drinking water), but not consider contribution from other sources such as dietary or inhalation exposure; or studies might report arsenic exposure concentrations from a particular source (e.g., a community water supply) rather than individual exposure levels. Furthermore, these source concentrations might be estimated from samples taken over a limited period or a single time point and extrapolated to lifetime exposures. Therefore, studies with exposure data for individuals are assumed to introduce less uncertainty to associations between health effects and inorganic arsenic.

To complement the conceptual model described in this document and to inform hazard identification and dose-response analyses, EPA will evaluate arsenic exposures and exposure pathway considerations. Based on NRC's recommendation, urinary arsenic concentrations of 1–5 μg/L (summing inorganic, monomethyl, and dimethyl arsenic forms) will be assumed a reasonable estimate of background for the U.S. population. If necessary, descriptions of background might be generated for non-U.S. populations, based on available data. Supplementary materials for exposure pathway considerations will include:

- evaluation of the applicability of a physiologically based pharmacokinetic model(s) to estimate biomarkers of exposures such as inorganic arsenic or its metabolite levels in urine;
- use of physiologically based pharmacokinetic model(s) for the forward estimation of biomarkers of exposures (e.g., urine levels) and reverse calculations of total ingested inorganic arsenic levels related to risk-estimated biomarkers; and

- consideration of dosimetry and pharmacokinetic issues concerning analyses of developmental effects.

If the AOP/N analysis suggests a direct and quantifiable relationship between a key event and an adverse outcome, the key event could be selected for dose-response analyses. Otherwise, human or animal toxicology or in vitro data might provide a mechanistic understanding and interpretation of low-dose effects observed in epidemiologic studies. Specifically, these data could be used to inform variability and uncertainty in the dose-response analysis and selection of dose-response modeling approaches.

Variability and Uncertainty in Dose-response Analyses

Variability and uncertainty are important components of risk characterization. Variability represents the diversity or heterogeneity of a factor that can influence the response within an individual or across a population. Uncertainty represents unavailable or incomplete information on a specific variable that can influence the analyses. Regarding variability, many factors are instrumental in determining an individual's risk from exposure, including concurrent background exposures to other chemicals and the individual's biological susceptibility due to genetic, lifestyle, health, and other factors. In turn, population responses to chemical exposures depend on the distribution of these varying individual determinants in the population. The *IRIS Toxicological Review of Inorganic Arsenic* will use observational and mechanistic data, as feasible, to inform the variability and uncertainty characterizations. In addition, EPA will develop sensitivity analyses for life stage and potentially other factors that influence dose-response analyses for inorganic arsenic.

Dose-response Modeling Approaches

Dose-response analyses will be performed on endpoints for which inorganic arsenic is determined "causal" or "likely causal." NRC and others have recommended using approaches that result in a probabilistic characterization of risk as a function of dose, while incorporating issues of susceptibility. The use of probabilistic approaches to incorporate information on uncertainty and variability into the derivation of human health toxicity values for cancer and noncancer endpoints will lead to an improved use of the available scientific information and promotion of research to characterize these factors. The approaches used in the *IRIS Toxicological Review of Inorganic Arsenic* are specific to inorganic arsenic at this time; adopting such an approach does not necessarily signal a change from current assessment approaches for other NCEA products.

The general approach EPA plans to take for this Toxicological Review is described as three tiers of increasing complexity: Tier 1 represents a standard approach to be applied to most endpoints, and Tiers 2 and 3 represent methods to be applied if warranted for selected endpoints.

Generally, Tier 1 dose-response will be restricted to a relatively small set of simple models, and risk estimates will be derived based on the units of exposure or intake the authors report. No attempts will be made to incorporate multiple sources of arsenic or to compare studies based on different dose metrics. Outputs of Tier 1 analyses could include estimates of low-dose points of

departure (such as benchmark doses and lower limits of benchmark doses) that have been used in EPA's traditional approach for deriving cancer slope factors and noncancer reference doses. A goal of Tier 1 is to help generate screening-level risk estimates to support approximate comparisons of risk across studies, and to guide the selection of data sets for higher-tier analyses.

As illustrated in Table 3-3, Tiers 2 and 3 differ from the more simplified Tier 1 analyses regarding the types of study data analyzed (individual instead of grouped data), the numbers of studies evaluated (the higher tiers accommodate pooled and meta-analyses where feasible), and dosimetric methods to be employed. Also, the range of model forms is wider in Tiers 2 and 3, which both incorporate model averaging where feasible. The higher tiers also will use more advanced approaches, including explicitly probabilistic models, to evaluate uncertainty and variability in dose-response. Bayesian analyses of single data sets, or meta-regression based on data from multiple studies, might be used to derive fully probabilistic risk estimates in either Tier 2 or Tier 3. A distinguishing feature of a Tier 3 approach is application of Bayesian (Markov Chain Monte Carlo) approaches to generate distributional outputs based on the data and the assumed prior probabilities for models and distributions of model parameters. Depending on data availability, EPA might also use empirical data or physiologically based pharmacokinetic models to compare studies that present risks as a function of exposure with those that present risks versus biomarkers, such as urinary arsenic. The range of model forms also is more extensive in the higher tiers, with approaches "fine-tuned" to specific data sets as appropriate. As feasible, mechanistic data will inform model selection and evaluation in the higher tiers.

Extrapolation for Dose-response Analyses

NRC recommended using observed data to characterize dose-response relationships. They also recommended limited extrapolation, to within an order of magnitude of observed data, using the modeled shape of the dose-response relationship to provide data-informed estimates of the potential dose-response relationship below the range of observation. Model choices will allow for nonlinear or threshold phenomena, as supported by the data. NRC further recommended characterizing dose-response relationships down to (but not necessarily at exposures below) background levels, which they estimated to be 1–5 μg/L inorganic arsenic in urine for U.S. populations. NRC indicated that the risks below background concentrations should be characterized to the extent feasible but also assumed the needs of risk assessors would be met if risk can be characterized *down to* background concentrations. Extrapolations in the Toxicological Review will be informed by these recommendations. As feasible, EPA will consider statistical methods and measures such as confidence or prediction limits that might help develop these extrapolations; details will be provided in the supplementary materials for EPA's dose-response analyses. Biological considerations also will inform model choice and extrapolation, as feasible.

Table 3-3. Summary of proposed inorganic arsenic dose-response analysis tiers

Dose-Response Element	Approach	Tier 1	Tier 2	Tier 3
Type of study data	Grouped exposure or outcome, or both	✓	✓	✓
	Individual exposure, outcome, covariates		✓	✓
Number of studies evaluated	One at a time	✓	✓	✓
	Multiple studies (meta-analysis and similar)		✓	✓
Dosimetry	Exposure or intake metrics as reported by authors	✓		
	Intake metrics including exposures from multiple sources		✓	✓
	Biomarker data	✓	✓	✓
	Intraconversion of intake/biomarker metrics based on empirical data, physiologically based pharmacokinetic models		✓	✓
Dose-Response Model Forms	Standard parametric models (Poisson regression, benchmark-dose type models, etc.)	✓		
	Complex parametric and nonparametric models (random effects, etc.)		✓	✓
Dose-Response Modeling Methods	Conventional (primarily maximum likelihood estimate)	✓	✓	
	Bayesian (Markov Chain Monte Carlo)			✓
	Model averaging		✓	✓
Output Risk Metrics	Points of departure, reference doses, low-dose slope factors, or equivalent	✓		
	Model-based risk estimates		✓	✓
	Fully probabilistic risk estimates			✓
Uncertainty and Variability Analyses	Primarily qualitative, evaluation of risk differences across models, studies	✓		
	Risk for subpopulations based on quantitative estimates of sensitivity (absorption, distribution, metabolism, excretion, etc.)		✓	✓
	Probabilistic modeling of exposure, pharmacokinetic, and prior distribution uncertainty as supported by data			✓
Low-Dose Extrapolation	Within range of study data only	✓		
	Statistical confidence limits on predicted risks		✓	✓
	Quantitative consideration of adverse outcome pathway information, individual variability			✓

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Appendix A. Evidence Integration

The Evidence-Integration Process

The objective of hazard identification is to answer systematic review questions of the form: "What does the evidence indicate about the relationship between [the agent] and [a specific health outcome] in humans?" Evidence integration is a process that answers such questions by combining inferences from different lines of evidence: human, animal, and mechanistic. IRIS assessments integrate evidence through a structured process that involves scientific judgment.

The evidence-integration process considers the human and animal evidence and then evaluates whether the animal evidence supports, does not support, or is irrelevant to a conclusion of a health hazard to humans. Mechanistic evidence, if available, can have two distinct uses in hazard identification: to evaluate the relevance of animal evidence to humans or to augment the evidence in humans or animals by establishing the occurrence of precursor events that are attributable to the agent.

State-of-the-art approaches to evidence integration apply a standardized approach for grading the strength of the evidence and use clear and consistent summative language (NRC, 2011). As the IRIS Program evaluates multiple health outcomes of many chemical agents, the terms used in these conclusions should be consistent across health outcomes. The goal is clear and consistent communication of hazard conclusions, maintaining the rigor and transparency that systematic review brings to the early steps of an assessment.

Aligning Different Lines of Evidence

In IRIS assessments, each major class of health outcome (e.g., cancer, reproductive toxicity, neurotoxicity, respiratory-tract toxicity, liver toxicity) can be the subject of a separate exercise in evidence integration. In practice, drawing inferences at a finer level of specificity of effect (e.g., learning and memory, pregnancy outcomes) and then using these inferences to draw conclusions about the major health outcomes often makes sense. Human studies often enable the synthesis of evidence for specific health outcomes (e.g., separately for breast cancer and colorectal cancer, or for fetal cardiac defects and low birth weight).

The question of site concordance between animal species or between animals and humans, however, complicates the process of evidence integration. For example, liver tumors in one animal species can be predictive of carcinogenic potential in other species, but not necessarily in the liver. Similarly, malformations at one anatomical site in animals suggest the potential for developmental toxicity that could appear in another form in humans. In such cases, site-specific human inferences would be integrated with animal inferences across multiple sites (e.g., cancer observed at any site in animals overall could support an inference of breast cancer observed in humans). Even so, for

some health outcomes, toxicological understanding might be sufficient to justify the integration of human and animal evidence at a site-specific level.

A similar complication can arise if the human and animal studies investigate related agents. For example, human studies could involve exposure only to mixtures of related compounds, while the animal and mechanistic studies investigate the compounds individually. In this case, mixture-related human findings would be integrated with compound-specific animal and mechanistic findings (e.g., adverse effects observed in animals for nickel sulfate and nickel oxide could support an inference in humans for nickel compounds overall).

Synergy can occur through the synthesis of inferences from different disciplines. Initial views of one type of evidence can change when other lines of evidence are considered. For example:

- When the human evidence has alternative explanations, animal or mechanistic evidence can strengthen or diminish the plausibility of some explanations of the human evidence.
- When uncertainty exists as to whether a response in animals or humans is dose related, information on the occurrence of precursor events can add to or subtract from the plausibility of the response.
- When the animal response is strong, evidence establishing that the mechanisms underlying the animal response does not operate in humans can support the view that the animal response is irrelevant to humans. In this case, the animal response provides neither an argument for nor an argument against a conclusion of hazard to humans.
- Similarly, when general knowledge in the field indicates that animals are not a suitable model for a specific human disease (e.g., no animal model is accepted for human prostate cancer), the animal evidence is irrelevant and provides neither an argument for, nor an argument against, a conclusion of hazard to humans (e.g., negative results for prostate cancer in animals is not an argument against the possibility of prostate cancer in humans).
- When the evidence across different animal species or human populations seems inconsistent, evidence that different mechanisms or metabolites operate in different species can provide coherence to the overall results (e.g., evidence showing that positive results occur in, and only in, species that form a particular metabolite can explain a mix of positive and null results in different species).

The Evidence-Integration Narrative

The evidence-integration narrative presents the reasoning behind the evidence-integration process. The evidence-integration narrative assembles the major findings from human studies, animal studies, and mechanistic studies for each major class of health outcome. The evidence-integration narrative:

- presents the conclusions from each line of evidence,
- 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, and
- integrates all lines of evidence to characterize the agent's association with each health outcome.

The evidence-integration narrative should cite the major items of evidence that argue for a hazard within each evidence stream versus the major items of evidence that argue against the hazard. Subsequent discussion should attempt to resolve apparent inconsistencies; finding coherence across results would increase confidence in the overall conclusion. For example, a mix of positive (i.e., increased incidence of endpoint) and null (i.e., no increased incidence of endpoint) could result from differences in internal dose of a key metabolite. Conversely, unexplained inconsistency would indicate gaps in knowledge.