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Draft Development Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Inorganic Arsenic

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Office of Research and Development
National Center for Environmental Assessment
Washington, D.C.

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PREFACE

EPA has released information pertinent to the development of the Toxicological Review of Inorganic arsenic. The information in this document provides an overview of EPA's assessment approaches and scientific information that EPA will consider during the development of the draft Toxicological Review of Inorganic arsenic. The approaches and scientific information were informed by the National Research Council's (NRC, 2013) Interim Report entitled, *Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic*. Over the next several months, EPA will continue to release to the public scientific information and examples of how the approaches described below are implemented. Due to the large scientific database associated with health effects related to inorganic arsenic exposure, the scientific information contained in this package is extensive. EPA is currently developing approaches to efficiently represent the scientific information into an assessment that is both complete and concise.

EPA has identified several topics for discussion regarding the development of EPA's draft Toxicological Review of Inorganic Arsenic (cancer and noncancer effects). These general topics are described in greater detail below. Key science issues to be discussed can be found on the IRIS Public Meetings website (http://www.epa.gov/ncea/iris/publicmeeting/).

This information includes the following:

1. **Assessment Development Plan (ADP) for the Toxicological Review of Inorganic Arsenic** – The ADP contains a conceptual model and an analysis plan. Generally, the ADP provides scoping information, assumptions, and EPA's approach for developing the Toxicological Review of Inorganic Arsenic. The ADP utilized information and needs identified during scoping meetings held for Agency partners and public stakeholders (http://www.epa.gov/iris/irisworkshops/arsenic/meetings.htm). In 2013, NRC (http://www.nap.edu/catalog.php?record_id=18594) reviewed EPA's draft ADP. The NRC provided support for many of EPA's approaches contained in the document and recommendations as to how EPA should revise the ADP. EPA has incorporated NRC's recommendations in the current draft ADP.

2. **Literature Search Strategy and Systematic Review for Development of the Toxicological rReview of Inorganic Arsenic** – A computerized keyword search of PubMed, Web of Science, and Toxline using search terms is presented with

search updates conducted through April 2014. Health effects cluster determination was conducted using natural language processing to group studies based on the similarity of their titles and abstracts and then clustering references around known relevant "seed" studies to identify a subset for further review. The literature search for arsenic will be periodically updated. *A cut-off date for the draft assessment submitted for public comment will be July 2014*. The references identified in the updated literature search will bypass the natural language processing step and enter into primary screening. Similarly, references recommended by Agency partners, public stakeholders, or reviewers will undergo secondary screening, bypassing both natural language processing and primary screening. All of the screening process results and studies identified through this literature search will be available on EPA's HERO database (http://hero.epa.gov).

3. **Summary of Literature Identified to Support Hazard Identification for Inorganic Arsenic** – Following categorization by title and abstract, studies were further evaluated through full text review. The purpose of the full text review was to identify studies that would be relevant to hazard identification for inorganic arsenic; this review was not an exclusion step. All epidemiology and toxicology studies identified as likely to contain information supporting hazard identification based on title and abstract review were further characterized to identify characteristics of the study design and the health effects reported in the study. Based upon the full text review, epidemiology and animal toxicology studies considered relevant to hazard identification were selected for risk of bias evaluations. References were categorized by subject based on manual review of the title and abstract of each, thereby identifying the toxicology and epidemiology studies that support the identification of a human hazard for inorganic arsenic. Characterization of studies and development of endpoint identification tables was conducted using the previously identified toxicology and epidemiology studies, resulting in an overview of the available literature for hazard identification.

4. **Summary of Risk of Bias Evaluations for Inorganic Arsenic Epidemiologic Studies** – Risk of bias evaluations are not exclusion criteria, rather, they represent evaluations that will determine the primary literature considered for hazard identification. Studies with a high risk of bias may provide supporting evidence, but will not be presented in evidence tables. Risk of bias has been evaluated using a modified draft Office of Health Assessment and Translation

(OHAT) approach (NTP, 2013). The OHAT approach identifies studies and extracts data from all of the available studies, regardless of potential risk of bias. The risk of bias evaluations are a series of questions addressing selection bias, performance bias, attrition/exclusion bias, detection bias, and selective reporting bias applied to each study. For each of the risk of bias elements, individual studies are assessed using a 4-point scale from high to low risk of bias. Risk of bias ratings for the individual questions will be used to tier the studies as high to low risk of bias. Studies identified as low risk of bias will subsequently have data extracted and considered principal evidence for developing hazard identification conclusions; and high risk of bias studies may provide supporting evidence. Examples of potential health hazards include: lung, skin, and bladder cancer; ischemic heart disease; skin lesions; prostate and renal cancer; diabetes; nonmalignant respiratory diseases; pregnancy outcomes; neurodevelopmental toxicity; immune effects; liver and pancreatic cancer; renal disease; hypertension; and stroke.

5. **Evidence tables for Inorganic Arsenic Epidemiologic Studies** – Data from low risk of bias studies have been extracted and presented in evidence tables. Evidence tables present data from studies related to a specific outcome or endpoint of toxicity. At a minimum, these evidence tables include the relevant information for comparing key features such as study design, exposure metrics, and dose-response information. Evidence tables will serve as an additional method for presenting and evaluating the suitability of the data to inform hazard identification for inorganic arsenic. For each health effect domain, a series of specific questions or criteria will be developed to help inform the suitability of the data for hazard identification and potential utility for dose-response assessment. Criteria specific for each health effect domain are needed because experimental design considerations or data analysis techniques may have a greater impact on particular health effect data.

6. **Summary of Risk of Bias Evaluations for Inorganic Arsenic Animal Studies** – Animal studies for hazard identification have been identified by screening the health effect cluster from the comprehensive literature search product, as well as by primary screening of the literature search updates. Toxicological data has been evaluated using a modified approach for risk of bias based upon the OHAT approach (NTP, 2013). Similar to the epidemiology studies, risk of bias evaluations will not be used to exclude studies, rather, these evaluations will be used to determine potential bias in the data. For each of the risk of bias elements,

individual studies are assessed using a 4-point scale from high to low risk of bias. Risk of bias ratings for the individual questions will be used to tier the studies as high to low risk of bias. Low risk of bias studies will be considered the principal data, subsequently will have data extracted and will be presented for comparison with epidemiologic data in evidence tables. High risk of bias studies may provide supporting evidence. To date, EPA has conducted risk of bias evaluations for immune, liver and developmental effects based upon the recommendation from NRC (2013) that animal studies for these health effects may provide critical information. EPA will evaluate health effects data from animal studies for additional endpoints in the near future.

7. **Evidence tables for Inorganic Arsenic Animal Studies** – Data from low risk of bias studies have been extracted and presented in evidence tables. Evidence tables present data from studies related to a specific outcome or endpoint of toxicity. At a minimum, these evidence tables will include the relevant information for comparing key features such as study design, exposure metrics, and dose-response information. Evidence tables will serve as an additional method for presenting and evaluating the suitability of the data to inform hazard identification for inorganic arsenic. For each health effect domain, a series of specific questions or criteria will be developed to help inform the suitability of the data for hazard identification and potential utility for dose-response assessment. Criteria specific for each health effect domain are needed because experimental design considerations or data analysis techniques may have a greater impact on particular health effect data.

8. **Mode of Action (MOA) Literature Search Strategy for the Toxicological Review of Inorganic Arsenic** – Mechanistic data will be identified through natural language processing based on previous human health assessments of inorganic arsenic, as well as focused literature searches. For hazard identification, human relevance will be informed by mechanistic data. Studies identified through this literature search will be available on EPA's HERO database (http://hero.epa.gov).

9. **Inorganic Arsenic Mode of Action (MOA) Hypothesis Summaries** – To facilitate discussions at the bimonthly meeting, EPA has developed qualitative hypothesis summaries for several potential MOAs associated with health effects of inorganic arsenic. The hypothesized MOAs were selected based on available information from authoritative reports and reviews on inorganic arsenic MOA (Cohen et al., 2013; NRC, 2013; Jomova et al., 2011; Kitchin and Conolly, 2010;

Prins, 2008). Potential MOAs may include, but are not limited to, cytotoxicity and regenerative proliferation, oxidative stress following generation of reactive oxygen species and depletion of antioxidant enzymes, and alteration of epigenetic mechanisms (e.g., DNA methylation). These qualitative MOA hypothesis summaries briefly summarize the available mechanistic data for several potential modes of action relevant to cancer and non-cancer health effects associated with inorganic arsenic. Five examples of MOA hypothesis summaries are included in this package to facilitate discussion on MOA-relevant topics detailed in Section 1. The information presented in these example summaries is not comprehensive, but intended to organize useful discussions with Agency partners and public stakeholders. Based on information provided by reviewers of these materials and the results of EPA's MOA literature search (outlined in Section 10), these MOAs will be refined and additional documentation will be added. Additional MOAs may also be identified through discussion in the bimonthly meeting. Information on MOAs associated with health effects that are causal or likely causal related to inorganic arsenic exposures will support the development of an adverse outcome pathways (AOP). AOPs characterize existing scientific information between a molecular initiating event and an adverse outcome for individual and population level responses. The AOP framework will not displace the mode of action framework defined by the Cancer Guidelines (U.S. EPA, 2005), but be inclusive of mode of action analysis. More information on the use of MOA analyses and AOP framework in the inorganic arsenic IRIS assessment is available in the ADP (Section 1).

10. **Preliminary Mechanistic and Susceptibility Data Tables** – Mechanistic data will be considered during hazard identification and dose-response analysis. For hazard identification, qualitative MOA analyses informed by the MOA hypothesis summaries (Section 9) will be developed for each health endpoint. Qualitative MOA analyses will be organized using tables that may support AOP development. Examples of this organization are provided in summary tables. The summary tables currently contain data relevant to a particular MOA, which may relate to multiple health effects. The data used to create these summary tables is available in the EPA HERO database (http://hero.epa.gov). These qualitative MOA analyses will be used to inform causal determinations for individual health effects.

For causal or likely causal health effects, mechanistic and susceptibility data will be organized into an AOP. These AOP analyses will be used to inform the dose-response

analyses, including potential impact of susceptibility factors on the dose-response. Preliminary data on some potential susceptibility factors are provided to facilitate further discussion.

The extent to which an AOP can inform dose-response analyses is dependent upon the available mechanistic data. Data may be insufficient to support an AOP for particular health effects. If the mode of action is unknown, the adverse outcome will be considered relevant to humans. Data gaps preventing a complete AOP will be considered sources of uncertainty. Mechanistic data or AOPs will not be a requirement for evaluating observed health effects due to exposure to inorganic arsenic.

1 ASSESSMENT DEVELOPMENT PLAN

1.1 Executive Summary

The U.S. Environmental Protection Agency (EPA) National Center for Environmental Assessment (NCEA) is developing a state-of-the-science toxicological review on inorganic arsenic for the Integrated Risk Information System (IRIS) Program. During development of the toxicological review, IRIS is committed to engaging Agency partners and public stakeholders. Agency partners and public stakeholders have been active participants in the scoping and planning process. On the basis of their recommendations, as well as Congressional mandate, the toxicological review will examine the cancer and noncancer effects from oral, inhalation, and dermal inorganic arsenic exposure. The IRIS toxicological review will consist of hazard identification and dose-response assessment. Exposure assessment and risk characterization are outside the scope of an IRIS toxicological review.

Key Points - Executive Summary

- State-of-the science toxicological review on inorganic arsenic to be developed by EPA
- Congressional mandate directs EPA to contract with NRC to conduct a review of inorganic arsenic toxicological review
- Toxicological review consists of hazard identification and dose-response
- Cancer and noncancer effects of inorganic arsenic exposure will be considered
- Oral, inhalation, and dermal routes of inorganic arsenic exposure will be examined
- Assessment development plan serves as the problem formulation for the toxicological review
- Assessment development plan consists of conceptual model and analysis plan
- Assessment development plan revised to incorporate NRC (2013) recommendations
- Multiple opportunities to engage Agency partners and public stakeholders

This assessment development plan serves as the problem formulation for the toxicological review and consists of two components: a conceptual model and an analysis plan. The conceptual model identifies specific relationships examined in the toxicological review, as well as those relationships which are beyond the scope of the toxicological review. Relationships outlined in the conceptual model will be analyzed and interpreted using approaches described in the analysis plan. The analysis plan has been substantially revised to incorporate NRC recommendations in the interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic" (NRC, 2013). Both the conceptual model and analysis plan may be revised as new data, methods, or risk management needs arise.

Accordingly, the assessment development process includes multiple opportunities for Agency partners and public stakeholders to provide input.

1.2 Background

Inorganic arsenic is a naturally occurring element widely distributed throughout the Earth's crust. In addition to natural sources, industrial activities such as coal combustion and smelting operations can release inorganic arsenic. Low concentrations of inorganic arsenic are found in water, food, soil, and air. This prevalence increases the potential for human exposure; therefore, characterization of the human health impacts of inorganic arsenic exposure is important to Agency partners and public stakeholders.

Key Points - Background

- 1988: EPA published an IRIS assessment of inorganic arsenic
- 2003: EPA began updating IRIS assessment of inorganic arsenic
- 2005: EPA released draft IRIS assessment of inorganic arsenic (cancer health effects of oral exposure) for public comment and peer review
- 2010: EPA released a revised draft IRIS assessment of inorganic arsenic (cancer health effects of oral exposure) for public comment and peer review
- 2011: Congress directed EPA to contract with the NRC to conduct a review of EPA's draft inorganic arsenic assessment
- 2013: NRC released interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic" providing recommendations for developing draft inorganic arsenic assessment

1.2.1 Previous EPA Assessments on Inorganic Arsenic

EPA completed a health assessment of inorganic arsenic in 1988. In 1996, EPA requested that the National Research Council (NRC) evaluate the inorganic arsenic database and recommend revisions to the 1988 assessment. In response, the NRC published the 1999 report "Arsenic in Drinking Water" (NRC, 1999).

In 2000, EPA requested NRC update their 1999 report as well as review the Primary Drinking Water Standard for Arsenic. In response, NRC published "Arsenic in Drinking Water - 2001 Update" (NRC, 2001), which concluded that (1) the database on the human carcinogenic effects of inorganic arsenic was adequate for risk assessment, (2) lung and bladder cancer should be the focus of inorganic arsenic risk assessment, and (3) epidemiology studies from southwestern Taiwan are the most appropriate dataset. Also,

in 2001, EPA established the Primary Drinking Water Standard which set a maximum contaminant level of 10 µg/L in drinking water. In 2003, the EPA Office of Research and Development and Office of Water decided to jointly revise the 1988 IRIS inorganic arsenic assessment to incorporate recommendations from the 1999 and 2001 NRC reports.

In 2005, the assessment was divided into two parts – one focused on noncancer outcomes and the other focused on cancer outcomes. In 2005, IRIS released a draft assessment focused on cancer health effects following oral exposure to inorganic arsenic for public comment and review by EPA's Science Advisory Board (SAB). The SAB provided recommendations in 2007 (SAB, 2007) and EPA revised the draft inorganic arsenic assessment to incorporate the SAB recommendations. The revised draft IRIS assessment focused on cancer health effects following oral exposure to inorganic arsenic and was released for public comment and review by the SAB in 2010 (U.S. EPA, 2010). The SAB provided comments and recommendations on the revised draft IRIS assessment in 2011 (SAB, 2011).

1.2.2 Congressional Directive for EPA Toxicological Review of Inorganic Arsenic

EPA received additional direction from Congress in December 2011, through The Consolidated Appropriations Act (U.S. Congress, 2011), to contract with the NRC to conduct a review of EPA's draft inorganic arsenic assessment considering both cancer and noncancer hazards from oral exposure to inorganic arsenic. In accordance with this Congressional mandate, the draft inorganic arsenic assessment will be reviewed by the NRC. The NRC review consists of two phases. The first phase consists of NRC meetings discussing the scope and key science issues for the draft assessment. Upon completion of this phase, the NRC will provide recommendations for developing the draft assessment. EPA will incorporate, where possible, the NRC recommendations and draft an inorganic arsenic assessment of cancer and noncancer hazards. The draft assessment will be provided to the NRC for the second phase of their review. In this second phase, NRC will provide critical scientific peer review of the draft assessment, according to their review criteria.

1.2.3 Overview of NRC Interim Report "Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic"

The first phase of the NRC review began in July 2012 and was completed in November 2013. As part of first phase of the NRC review, EPA provided the NRC draft materials for comment. These draft materials included planning and scoping documents as well as a draft ADP outlining proposed approaches for literature searches, literature evaluation, hazard identification, and dose-response analyses. In November 2013, the NRC delivered the interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic" (NRC, 2013). The interim report provided recommendations for the toxicological review of inorganic arsenic on key science issues. These scientific recommendations are summarized in Table 1-1 and discussed further in the revised conceptual model (Section 1.4) and analysis plan (Section 1.5).

Table 1-1 Summary of NRC Recommendations on IRIS Assessment of Inorganic arsenic

NRC Recommendation	ADP Section
Exposure considerations - consider contribution of inorganic arsenic intake from rice in South Asian and Taiwanese population	1.5.1 Approaches to Source Considerations
Exposure Considerations - consider probabilistic approach to estimate daily intake from rice to account for variability in rice consumption and concentration of inorganic arsenic in rice	1.5.1 Approaches to Source Considerations
Exposure Considerations - IRIS assessment can benefit from examining studies which provide estimates of both external exposure and biomarker of exposure data are provided	1.5.3 Approaches to Exposure Pathway Considerations
Exposure Considerations - Hazard identification should take into account that some people are more susceptible because of relative inability to metabolize inorganic arsenic	1.5.4 Approaches to Receptor Considerations
IRIS Assessment Development Plans - EPA should design mode of action tables	1.5.5 Approaches to Endpoint Considerations
IRIS Assessment Development Plans - for microarray/NextGen sequence data – for conclusions based solely on expression, need detailed analysis of data supporting conclusion, including pre-processing and statistical analysis, which will require raw data	1.5.5 Approaches to Endpoint Considerations
IRIS Assessment Development Plans - Meta-analyses for hazard identification if ≤ 3 peer-reviewed studies; meta-analyses for dose-response if ≤ 3 doses tested	1.5.5 Approaches to Endpoint Considerations
IRIS Assessment Development Plans - As part of systematic review process, risk of bias should be evaluated using established guidelines	1.5.5 Approaches to Endpoint Considerations

NRC Recommendation	ADP Section
IRIS Assessment Development Plans - Conducting meta-analyses of aggregated data from published studies is an appropriate alternative to analyzing raw data for individual level meta-analyses	1.5.5 Approaches to Endpoint Considerations
Hazard identification - For non-cancer effects, consider diseases with high prevalence in U.S. population to determine if inorganic arsenic contributes to disease burden [e.g. cardiovascular disease (CVD), respiratory disease, kidney disease, diabetes]	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Observation epidemiologic studies preferred for determining association between inorganic arsenic exposure and skin lesions	1.5.5 Approaches to Endpoint Considerations
Hazard identification - EPA consider skin studies that have histologic specificity	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Focus on human studies that investigate coronary arterial disease, myocardial infarctions, CVD, and overall CVD mortality…can exclude peripheral arterial disease based on dose-response and associations in populations with poor nutrition….cerebrovascular disease can be included…hypertension is less of a priority	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Critical synthesis of human population studies with mode of action underlying different non-malignant respiratory outcomes/phenotypes should be focus	1.5.5 Approaches to Endpoint Considerations
Hazard identification - US data on drinking-water arsenic (inorganic) and bladder cancer in US should be evaluated by EPA, particularly with respect to smoking	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Studies of incidence, rather than mortality, may better reflect the impact of inorganic arsenic on kidneys	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Essential to evaluate potential adverse effects on fetal and postnatal exposure to inorganic arsenic	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Effects of inorganic arsenic in elderly populations is a particular research need	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Recent epidemiologic studies supporting association between inorganic arsenic and diabetes at low to moderate concentrations should be carefully reviewed and included quantitatively	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Given evidence and burden of prostate disease in US men, should at least consider prostate cancer	1.5.5 Approaches to Endpoint Considerations
Hazard identification - Hazard assessment should include epidemiologic and experimental evidence and integrate mode of action where possible	1.5.5 Approaches to Endpoint Considerations

NRC Recommendation	ADP Section
Hazard identification - Strength of evidence judgments characterized using modified Hill (1965) criteria	1.5.5 Approaches to Endpoint Considerations
Mode of action - Rigorously examine epidemiologic studies using Hill (1965) criteria to examine appropriateness for risk assessment	1.5.5 Approaches to Endpoint Considerations
Dose-response Analysis - Evaluate data on multiple outcomes to assess whether they are appropriate for estimating health outcomes in range of epidemiologic observations	1.5.5 Approaches to Endpoint Considerations
Dose-response Analysis - Update selected health outcomes as new data becomes available	1.5.5 Approaches to Endpoint Considerations
Dose-response Analysis - Consider evidence of life-stage sensitivity when considering less-than-lifetime exposure	1.5.5 Approaches to Endpoint Considerations
Exposure Considerations - Dose-response relationship from epidemiologic studies concerning health effects of inorganic arsenic in drinking water should include likelihood that doses derived from drinking water alone does not represent the total inorganic arsenic dose	1.5.6 Approaches to Risk Metric Considerations
IRIS Assessment Development Plans - Meta-analyses for hazard identification if ≤ 3 peer-reviewed studies; meta-analyses for dose-response if ≤ 3 doses tested	1.5.6 Approaches to Risk Metric Considerations
IRIS Assessment Development Plans - Conducting meta-analyses of aggregated data from published studies is appropriate alternative to analyzing raw data for individual level meta-analyses	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - May be possible to model dose-response relationships from estimated relative risk associated with categories of exposure…may necessitate assessment of confounding by cigarette smoking…associations could be specific to histological type requires biomarker concentration	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Major consideration for respiratory mode of action should be epidemiologic and animal studies that identify potential pathogenic mechanisms in response to low/moderate inorganic arsenic exposures	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Important respiratory mode of action consideration is whether in utero/perinatal exposure poses significant risk of lung disfunction/disease	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Consider evidence that chronic inflammation and reactive oxygen species are central to pathogenesis of inorganic arsenic-induced CVD	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - For CVD, address potential uncertainties from differences between study population and general population	1.5.6 Approaches to Risk Metric Considerations

NRC Recommendation	ADP Section
Hazard identification – Mode of action analysis will need to consider that there may be multiple mechanisms by which inorganic arsenic can cause bladder cancer….crucial to assess exposure on an individual level and include biomarkers/relevant co-factors where possible….examine incidence rather than mortality and examine susceptible groups of the population	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Consider whether inorganic arsenic/diabetes have interaction effects on renal function and chronic kidney disease	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Data that can be used for dose-response concerning birth size and infant growth, possibly infant mortality	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - MAPK/extracellular signal-related kinase pathway should be considered as to whether it might be an underlying cause of learning deficits	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Recent epidemiologic studies supporting association between inorganic arsenic and diabetes at low to moderate concentration should be carefully reviewed and included quantitatively	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Both innate and adaptive immune responses should be considered	1.5.5 Approaches to Endpoint Considerations 1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Hazard assessment should include epidemiologic and experimental evidence and integrate mode of action where possible	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - With respect to mode of action, important to consider dose and time-dependence of exposure to key immunological events	1.5.6 Approaches to Risk Metric Considerations
Hazard identification - Important to consider timing with respect to life-stage, duration of exposure, and latent period for the health outcome	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Evaluate whether early life exposure may affect the risk of inorganic arsenic-related effects in adults	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Timing of exposure should be considered in evaluating epidemiologic studies for dose-response assessment	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - It is essential to evaluate sex differences in inorganic arsenic metabolism and toxicity to protect the most susceptible population	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Assessment should consider nutritional status of study populations when examining dose-response relationships reported in the epidemiologic literature	1.5.6 Approaches to Risk Metric Considerations

NRC Recommendation	ADP Section
Susceptibility Factors - Factors important to evaluating potential for inorganic arsenic to interact with background disease processes on a population level: overall mode of action and disease mechanism; prevalence of disease, prevalence of pre-clinical disease	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Consideration should be given to whether people may be vulnerable to effects because disease processes impair defense mechanisms or act in concert with inorganic arsenic mode of action	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - May be possible for non-cancer assessment to describe increased disease risk associated with any particular dose – if RfD derived, can be described as dose associated with particular increase in risk	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Consider whether dose-response will focus on population as a whole or involve separate assessments for general population and susceptible subgroups	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Plausible quantitative approach is sensitivity analysis to determine how smoking-interaction synergism changes potency calculation of dose-response	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Evaluation of size/nature of vulnerable populations will help determine if epidemiologic studies adequately capture these groups	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Co-exposure may be worth mentioning as additional mechanistic explanation to explain some endpoints associated with inorganic arsenic exposure; consider co-exposure to metals and PAH	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Helpful to assess how interacting metals/PAHs might co-occur in the epidemiologic study populations in comparison with target populations of risk assessment	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - Potency adjustment for susceptible populations is feasible if appropriate dose-response data are available in comparison with the general population	1.5.6 Approaches to Risk Metric Considerations
Susceptibility Factors - When sizeable population is vulnerable, it's reasonable to extend dose-response below range of observation by modest extrapolation	1.5.6 Approaches to Risk Metric Considerations
Mode of action - Identifying mode of action data gaps and their potential effects on ability to extrapolate to low exposures is important	1.5.6 Approaches to Risk Metric Considerations
Mode of action - Committee recommends following TCE and chloroform when beginning mode of action analysis	1.5.6 Approaches to Risk Metric Considerations

NRC Recommendation	ADP Section
Mode of action - Important aspect will be Mode of action for each observed health outcome, including supporting and contradictory evidence	1.5.6 Approaches to Risk Metric Considerations
Dose-response Analysis - 1-5 µg/L is reasonable estimate for US background	1.5.6 Approaches to Risk Metric Considerations
Dose-response Analysis - Derive risk estimates for health effects then derive risk-specific doses to address needs of analyses that would typically use a RfD…provide guidance on how RfD might be selected among risk-specific doses	1.5.6 Approaches to Risk Metric Considerations
Dose-response Analysis - Consider study-selection options to facilitate dose-response options, with preference to studies in low-moderate exposure ranges and using biomarkers of exposure	1.5.6 Approaches to Risk Metric Considerations
Dose-response Analysis - Common exposure metric is needed to integrate across studies	1.5.6 Approaches to Risk Metric Considerations
Dose-response Analysis - Use limited extrapolation by using modeled shape of the dose-response relationship to provide data-informed estimate of potential dose-response relationships below range of observation	1.5.6 Approaches to Risk Metric Considerations

The NRC also provided recommendations on the approaches proposed in the draft assessment development plan. The NRC recommendations on the proposed approaches are summarized below.

In the draft materials submitted to NRC for review, the EPA provided the NRC with a draft planning and scoping summary outlining the needs of EPA partners and public stakeholders for a toxicological review of inorganic arsenic. In addition, these materials highlighted EPA's commitment to communicate with Agency partners and public stakeholders throughout development of the draft toxicological review. The NRC commented that these materials clearly demonstrated that EPA is incorporating recommendations from previous NRC committees (NRC, 2011, 2009) to involve risk managers, risk assessors, and stakeholders early in the development process.

EPA also submitted draft materials to the NRC outlining approaches for (1) literature search and evaluation, (2) scope of hazard identification, (3) mode-of-action analyses, and (4) scope of the dose-response analyses. The NRC found that the draft plans for literature search and evaluations captured the salient information from epidemiologic studies, but indicated that similar approaches to animal and in vitro data could be important for mode-of-action analyses. The NRC further commented that the outlined approaches to incorporate systematic review further demonstrated that EPA is

incorporating recommendations from previous NRC committees (NRC, 2011, 2009). The NRC committee on inorganic arsenic recommended searching for studies on specific outcomes, with specific criteria including individual measures of inorganic arsenic exposure, inorganic arsenic measurement preceding outcome, and low-to-moderate exposure (<100 µg/L in water).

For hazard identification, EPA proposed evaluating the relationship between inorganic arsenic exposure and human health effects using a causal determination framework (U.S. EPA, 2013). The NRC supported this approach for hazard identification, recommending consideration of animal and mechanistic data as supporting the causal determination. The NRC also highlighted particular health end points of concern that should be evaluated for hazard identification. The NRC also supported EPA's use of evidence tables to present information. The NRC stressed the importance of explaining causal determination judgments in the synthesis text.

The NRC supported EPA's proposal to perform mode-of-action analyses on health endpoints considered "causal" or "likely causal." The NRC recommended possible consideration of "suggestive" endpoints to determine if mechanistic data supported a stronger causal association. The NRC agreed with EPA's proposal that even if a mode-of-action cannot be determined, health endpoints with "causal" or "likely causal" relationships with inorganic arsenic should undergo dose-response analysis.

Several dose-response analysis recommendations were provided by the NRC. The NRC recommended developing risk estimates across the array of health effects for which there is adequate epidemiologic evidence. The NRC also stated that dose-response analyses should be performed in the range of epidemiologic observations. When those data are unavailable, the NRC recommended using mechanistic data for extrapolation; however, the NRC cautioned that extrapolations become increasingly uncertain as they go further below the observed range. The NRC commented that the needs of assessing health risks can be facilitated by characterizing dose-response relationships down to background concentrations. The NRC recommended that EPA derive risk–specific doses, which would facilitate efforts to evaluate cumulative risk, conduct risk-benefit assessments, or comparative analyses.

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

EPA is developing an IRIS assessment of inorganic arsenic that incorporates the recommendations from the NRC. This new IRIS assessment of inorganic arsenic will examine the available scientific database on cancer and noncancer health effects from inorganic arsenic exposure.

1.3 Developing the Toxicological Review

Key Points - Development

- Collaborative approach to developing the toxicological review
- An iterative process informed through engaging Agency partners and public stakeholders
- Assessment development plan informed by planning and scoping phase
- Two products: conceptual model and analysis plan
- Posting to the IRIS database in 2016

1.3.1 Goals of the Assessment Development Plan

This assessment development plan describes the problem formulation for the toxicological review of inorganic arsenic. Problem formulation is an iterative process that identifies factors for consideration in the toxicological review. Goals of problem formulation include explaining the purpose of the toxicological review, defining problems for consideration, and outlining a plan for characterizing risk. The assessment development plan for inorganic arsenic consists of two products: a conceptual model (Section 1.4) and an analysis plan (Section 1.5).

A conceptual model considers the sources, stressors, exposure pathways, receptors, endpoints, and risk metrics that may be evaluated in the toxicological review. The conceptual model provides a starting point to integrate the available data and outline relationships between these features. On the basis of scientific judgement and the needs of Agency partners and public stakeholders, the conceptual model identifies specific relationships to be considered in the toxicological review, as well as those relationships beyond the scope of the toxicological review. The decisions outlined in the conceptual model inform the analysis plan. The analysis plan outlines the analytic and interpretive approaches for evaluating the relationships identified in the conceptual model. As new data or risk management needs arise, it is anticipated that both the conceptual model and analysis plan will be revised.

In addition to the assessment development plan, EPA will develop several other documents supporting key elements of the toxicological review. These supplementary documents will provide additional information considered during development of the toxicological review. For instance, these supplementary materials may outline considerations used to make underlying conclusions or decisions presented in the toxicological review of inorganic arsenic. These supporting documents will be an opportunity to transparently document supplementary approaches and analyses used to develop the toxicological review of inorganic arsenic.

1.3.2 Agency Partner and Public Stakeholder Engagement

EPA is committed to engaging partners within the EPA and public stakeholders throughout the development of the toxicological review of inorganic arsenic. Agency partners (including other federal agencies) and public stakeholders (e.g., non-governmental organizations, industry groups, citizens, academia, etc.) have been active participants in planning and scoping meetings, identifying their needs for the toxicological review of inorganic arsenic, and making scientific recommendations for consideration. Multiple opportunities to provide feedback on the toxicological review, including public comment periods, webinars, and public reviews, have been, and will continue to be, important components of the development process. The participation of Agency partners and public stakeholders will ensure the toxicological review meets the needs of the risk management community and the public.

1.3.3 Transparency

EPA is committed to developing the toxicological review of inorganic arsenic in a transparent process. For the toxicological review, transparency means sufficient information will be available to understand the scientific rationale behind decisions, as well as reproduce methods used to identify and evaluate data. To ensure transparency to Agency partners and public stakeholders, materials used to develop the toxicological review (e.g., literature search products, evidence tables, exposure response arrays) will be made available for public review. In addition, future materials will provide links to EPA's HERO database (http://hero.epa.gov) to assist in transparency and public access to the peer reviewed literature citations. When possible, the toxicological review will present options for key decision points and provide rationale for choosing a particular option.

1.3.4 Timeline for Completion

The critical importance of inorganic arsenic to Agency partners and public stakeholders for the toxicological review is reflected in the unique approach NCEA has adopted for the toxicological review. The NRC recommendations outline a scientifically defensible approach for identifying, evaluating, and quantifying data on the health effects of inorganic arsenic. These recommendations will inform development of the toxicological review, as well as decisions on key science issues such as low-dose extrapolation and mode of action.

EPA will release an assessment development plan, literature search product, risk of bias evaluations, evidence tables, and qualitative mode of action hypothesis summaries for public input and discussion. These public discussions will inform draft development of the toxicological review of inorganic arsenic.

The draft toxicological review will undergo internal EPA review and review by other federal agencies and the public before being released for external peer review. External peer review of the toxicological review will be managed by the NRC. Following revisions and additional review by EPA and other federal agencies , the toxicological review is anticipated to post to the IRIS database in 2016. The current timeline for developing the toxicological review of inorganic arsenic is shown in Table 1-2.

Table 1-2 Draft Timeline for Development of the Toxicological Review of Inorganic Arsenic

PROPOSED PROCESS	TIMELINE
Internal EPA Partner Scoping and Problem Formulation Workshop	*Completed* *September 2012* http://www.epa.gov/iris/irisworkshops/arsenic/index.htm
Public Stakeholder Workshop – Planning and Scoping	*Completed* *January 2013* http://www.epa.gov/iris/irisworkshops/arsenic/index.htm
NRC Phase 1 Review	*Completed* *January – November 2013* http://www.epa.gov/iris/irisworkshops/arsenic/index.htm
IRIS Bimonthly Public Meeting	June 2014
Completed draft Inorganic arsenic Toxicological Review	Summer 2014
Complete Internal Agency Review	Summer 2014
Complete Interagency Science Consultation	Fall 2014
Release draft for Public Comment	Winter 2014
NRC Phase 2 review	Spring 2015
Complete NRC Phase 2 review	Winter 2015
Complete Internal Agency/Interagency Science Discussion	Spring 2016
Post to IRIS website	Summer 2016

1.4 Conceptual Model for the Toxicological Review

This conceptual model describes the rationale for developing the toxicological review of inorganic arsenic. The conceptual model consists of a written description and visual representation of the predicted relationships between inorganic arsenic exposure and human health effects. It is based upon the general conceptual model framework shown in Figure 1-1.

Key Points - Conceptual Model

- Scope of the toxicological review
- Identifies factors and endpoints to be evaluated in the toxicological review
- Written and visual representation of predicted relationships between exposure and human health effects
- Iterative process that can be refined during development of the toxicological review
- Revised in response to NRC recommendations in the interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic"

A conceptual model identifies the sources, stressors, receptors, exposure pathways, and health effects considered in the toxicological review. Predicted relationships between these factors are indicated in the visual diagram and described in the written portion of the conceptual model. Predicted relationships between inorganic arsenic exposure and human health effects may be revised as data become available; therefore, this conceptual model is considered a flexible framework that can be adapted as necessary during development of the toxicological review of inorganic arsenic.

1.4.1 Scope of the Toxicological Review

1.4.1.1 Summary

This section describes the scope of the toxicological review. Agency partner and public stakeholder input provided context for the development of the conceptual model. In addition, the conceptual model has been revised in response to NRC recommendations in the interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic" (NRC, 2013).

1.4.1.2 Components of an IRIS Toxicological Review

When considering scope, it is important to distinguish a risk assessment from an IRIS toxicological review. A risk assessment consists of four components: hazard identification, dose-response analysis, exposure assessment, and risk characterization. Comparatively, an IRIS toxicological review considers hazard identification and dose-response analysis. Although exposure assessment and risk characterization are beyond the scope of an IRIS toxicological review, information in the toxicological review of inorganic arsenic is anticipated to serve as part of the scientific basis for complete risk assessments of inorganic arsenic.

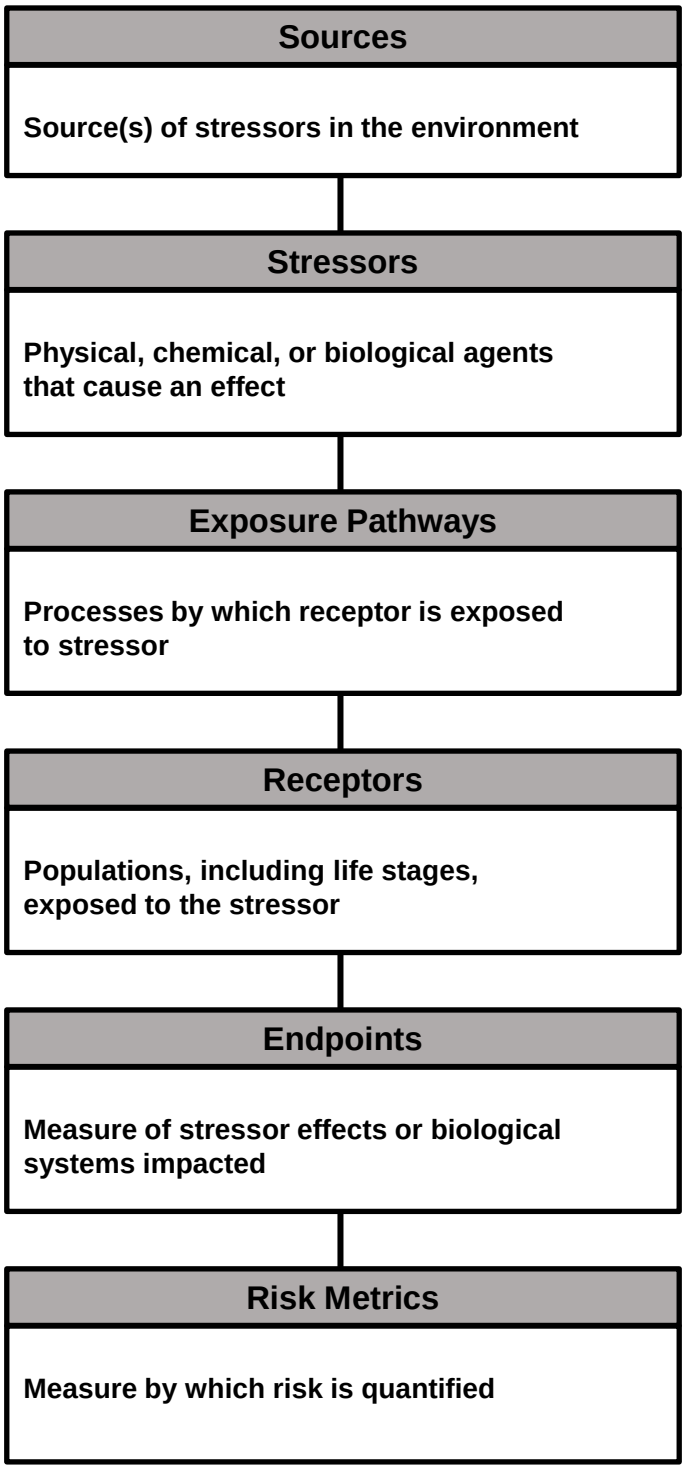


Figure 1-1 General Framework for the Conceptual Model

1.4.1.3 Agency Partner and Public Stakeholder Needs

The conceptual model for the toxicological review of inorganic arsenic was informed by Agency partners and public stakeholders. Agency partners and public stakeholders discussed their needs for the toxicological review of inorganic with the IRIS program in an internal meeting with Agency partners (September 2012) and a public stakeholder meeting (January 2013). Meeting reports are available online (http://www.epa.gov/iris/irisworkshops/arsenic/meetings.htm), and needs identified in those meetings are summarized here. Agency partners and public stakeholders have requested consideration of both naturally occurring and anthropogenic sources of inorganic arsenic. Stressors of interest to Agency partners and public stakeholders included inorganic arsenic as well as arsenic metabolites. Agency partners and public stakeholders requested consideration of oral, inhalation, and dermal exposure pathways. Humans were the principal receptor of interest, and Agency partners and public stakeholders recommended considering susceptible populations and life stages. When evaluating health endpoints, Agency partners and public stakeholders have requested consideration of both cancer and noncancer health effects, emerging health effects, and the need for mode of action and adverse outcome pathway analyses. With respect to the dose-response analyses, Agency partners and public stakeholders have indicated the need to estimate excess risk (i.e., risk above naturally occurring levels) at potential exposure levels for cancer and noncancer endpoints, including any potential risk at naturally occurring levels of inorganic arsenic. Agency partners and public stakeholders have recommended harmonization of cancer and noncancer dose-response analyses and multiple approaches to low-dose extrapolation (e.g., linear, nonlinear, probabilistic, etc.).

1.4.1.4 NRC Recommendations

The NRC interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic" (NRC, 2013) provided recommendations for developing the toxicological review. Specific recommendations are addressed in the analysis plan (Section 1.5). General recommendations on the conceptual model are summarized here.

The NRC indicated that there are numerous potential natural and anthropogenic sources of inorganic arsenic. The NRC indicated that the toxicological review would focus on inorganic arsenic as the stressor; however, the NRC recommended considering the contribution of metabolites of inorganic arsenic to health endpoints. The NRC recommended considering dietary sources of inorganic arsenic, particularly rice, as a potential exposure pathway. The NRC recognized that a major goal of the toxicological review is to identify hazards associated with chronic inorganic arsenic exposure in

humans and supported humans as the receptors of interest. When considering health effect endpoints, NRC recommended considering diseases with high prevalence in the United States. In addition, the NRC recommended that susceptibility factors to inorganic arsenic (e.g., life stages, impaired metabolism, sex, nutrition, or underlying disease state) should be considered. The NRC recommended that animal and in vitro data should be considered for mode-of-action analyses. The NRC also recommended that mode-of-action analyses should be conducted to inform confidence in the assessment of risk of inorganic arsenic at low doses. The NRC indicated that animal and in vitro studies are not the focus of dose-response analyses for inorganic arsenic. Rather, the NRC recommended that multiple human health outcomes should be evaluated for dose-response analyses. These evaluations should determine if data are appropriate for direct estimation of risk in the range of epidemiologic observation. The NRC recommended minimizing dose-response extrapolations beyond the observed evidence.

1.4.2 Sources

1.4.2.1 Summary

This section discusses natural and anthropogenic sources of inorganic arsenic. An assessment parameter that environmental exposure is widespread owing to both natural and man-made sources of inorganic arsenic is reached. The potential impact of this assessment parameter is that data limitations on inorganic arsenic sources may increase uncertainty in estimating exposure dose.

1.4.2.2 Naturally Occurring Sources of Inorganic Arsenic

Inorgnic arsenic is widely distributed throughout the Earth's crust and is present in more than 200 mineral species (IARC, 2009; ATSDR, 2007; Health Canada, 2006). Natural sources of inorganic arsenic result in naturally occurring, or "background," levels of inorganic arsenic in soil. Natural sources can also contribute to inorganic arsenic in water, particularly groundwater from wells in arsenic-rich geological formations. Volcanic activity releases, volatilization, and dusts are some natural sources of inorganic arsenic released in the atmosphere. It is estimated that approximately one-third of atmospheric inorganic arsenic comes from natural sources.

1.4.2.3 Anthropogenic Sources of Arsenic

Inorganic arsenic, primarily as arsenic trioxide, is released to the environment through mining, smelting, and burning fossil fuels (IARC, 2009; ATSDR, 2007). In addition, inorganic arsenicals are used in the manufacturing and processing of several products, including semi-conductors, textiles, ceramics, and pressure treated wood. To a lesser extent, organic arsenicals have been used as pesticides and veterinary drugs (Health Canada, 2006). Industrial, agricultural, and mining activities all contribute to anthropogenic sources of arsenic in the environment. Soil contaminated from mining activities, smelter waste, or agricultural pesticides can have arsenic concentrations higher than naturally occurring levels. Water levels of inorganic arsenic may be elevated through industrial effluents, mining, and smelting. Emissions from mining, smelting, burning fossil fuels, and use of organic arsenic pesticides contribute to elevated levels of arsenic in the air.

1.4.2.4 Considerations of Sources in the Toxicological Review

An exposure assessment is beyond the scope of this toxicological review. For the toxicological review, inorganic arsenic is considered to be widespread in the environment, with both natural and anthropogenic sources contributing to total arsenic exposure. Effects of environmental inorganic arsenic exposure will be considered independent from source considerations, such that endpoints will not be attributed to particular natural or anthropogenic sources.

1.4.2.5 Summary of Assessment Parameters for Sources

The assessment parameters for sources of inorganic arsenic exposure are summarized below. The rationale for the assessment parameter is described, as is the potential qualitative impact of this decision on the hazard identification.

Assessment Parameters for Sources	Rationale	Potential Impact on Toxicological Review
Inorganic arsenic exposure is widespread.	Natural and anthropogenic sources contribute to inorganic arsenic exposure.	Underestimation of exposure dose due to data limitations on inorganic arsenic sources in the environment.
Effects of inorganic arsenic exposure will be considered independent of source.	An exposure assessment is beyond the scope of the toxicological review.	Potential impact on the utility of the toxicological review for complete risk assessments.

1.4.3 Stressors

1.4.3.1 Summary

A stressor is a chemical, physical, or biological agent that causes an effect. In this section, the chemical properties of arsenic are summarized and candidate stressors for the toxicological review are considered. Based upon several considerations, inorganic arsenic is selected as the principal stressor in the toxicological review for the determination of risk metrics. Arsenic speciation was considered, resulting in an assessment parameter that valence state of inorganic arsenic in the environment is unlikely to impact health effects from exposure. The potential impacts of these assessment parameters are no estimation of health effects from environmental exposure to organic arsenic compounds, including metabolites of inorganic arsenic, and underestimating the potential impact of speciation on inorganic arsenic toxicity.

1.4.3.2 Chemical Properties

Elemental arsenic, or metallic arsenic, is a steel grey solid with chemical and physical properties intermediate between a metal and non-metal (IARC, 2009). Arsenic can exist in 4 oxidation states: -3, 0, +3, or +5. Because of its reactivity, elemental arsenic (oxidation state 0) is rarely found in the environment (ATSDR, 2007; U.S. EPA, 2006). Instead, arsenic is often found combined with other elements. These arsenic compounds, for the purposes of the toxicological review of inorganic arsenic, are organized into three

groups: organic arsenic compounds, arsine gas, and inorganic arsenic compounds (IARC, 2009).

Organic arsenic compounds have arsenic combined with carbon or hydrogen (ATSDR, 2007). Arsine gas specifically refers to AsH_3; however, the term arsine is often used to describe organic arsenic compounds where arsine is combined with aryl or alkyl groups. Inorganic arsenic compounds are those in which arsenic is combined with other elements such as oxygen, chlorine, or sulfur (ATSDR, 2007). Some arsenic compounds are shown in Table 1-3.

Table 1-3 Some Arsenic Compounds in the Environment

Chemical Name	Formula	CAS Number
Arsenic	As	7440-38-2
Arsenite	$As(OH)_3$	13464-58-9
Arsenate	$AsO(OH)_3$	7778-39-4
Arsenic trioxide	AS_2O_3	1327-53-3
Arsenic pentoxide	AS_2O_5	1303-28-2
Sodium arsenite	$NaAsO_2$	7784-46-5
Sodium arsenate	NA_2HAsO_4	7778-43-0
Arsine	AsH_3	7784-42-1
Arsenobetaine	$(CH_3)_3As^+CH_2CO_2^-$	64436-13-1
Dimethylarsine acid	$(Ch_3)_2HAsO_2$	75-60-5
Methanearsonic acid	$Ch_3H_2AsO_3$	124-58-3
Sodium dimethyl arsinate	$(CH_3)_2NaAsO_2$	124-65-2
Sodium methane arsonate	$CH_3NaHAsO_3$	2163-80-6
Trimethylarsine	$(CH_3)_3As$	593-88-4

1.4.3.3 Stressor Consideration – Organic and Inorganic Arsenic Compounds

All three groups of arsenic compounds were considered as candidate stressors for the toxicological review. Based upon toxicological and exposure considerations, as well as Agency partner and public stakeholder needs, inorganic arsenic was selected as the stressor for the toxicological review.

Total environmental arsenic consists of both organic and inorganic forms (WHO, 2011; ATSDR, 2007), although toxicity varies between organic and inorganic arsenic compounds. In general, direct exposure to organic arsenic compounds is considered less toxic than inorganic arsenic compounds (WHO, 2011; ATSDR, 2007). Inorganic arsenic is metabolized to organic arsenic in the human body, and some of these organic metabolites may play a role in exacerbating the effects of exposure to inorganic arsenic (WHO, 2011). While some of these organic arsenic metabolites are found in the environment, it can be hypothesized that effects of environmental arsenic exposure are largely attributable to the inorganic arsenic component of total arsenic.

Exposure considerations also support selecting inorganic arsenic as the stressor for the toxicological review. For instance, arsine is a highly toxic gaseous organic arsenical, but this volatile compound is unlikely to be found at levels of concern in the environment. Similarly, methylated arsenic compounds are assumed to be a minor component of atmospheric arsenic (WHO, 2000) and inorganic arsenic is the primary form found in drinking water and soil (IARC, 2009; Health Canada, 2006). Dietary exposure to organic arsenic can occur through consumption of fish and shellfish; however, the arsenobetaine or arsenocholine found in fish and shellfish are considered mostly non-toxic (Health Canada, 2006). These factors influenced the decision to consider inorganic arsenic the stressor for the toxicological review.

Agency partners and public stakeholders also influenced the consideration of stressors for the toxicological review. Some Agency partners and public stakeholders have indicated that total environmental arsenic is the stressor of concern, while others indicated that certain environmental organic arsenicals (e.g., pesticides or pressure treated wood compounds) influence their risk management decisions. The majority, however, emphasized that effects from inorganic arsenic, as the toxic moiety, are the primary considerations for their risk management decisions. Given the higher toxicity, relevant environmental exposure levels, and risk management needs, the toxicological review will consider inorganic arsenic the stressor of concern.

1.4.3.4 Stressor Consideration – Inorganic Arsenic Speciation

Oxidation state of inorganic arsenic was considered during stressor selection. Inorganic arsenic can be found in different oxidation states depending upon environmental conditions. Arsenic found in soil forms insoluble complexes which are relatively immobile; however, under reducing conditions arsenic may become soluble and enter into ground water (ATSDR, 2007). In an aquatic environment, inorganic arsenic exists primarily as a mixture of two oxidation states. The +5 oxidation state (arsenate or As[V]) is the most stable form in an oxygenated environment, whereas the +3 oxidation state (arsenite or As[III]) is the more common in a reducing environment (ATSDR, 2007). In air, inorganic arsenic also exists as a mixture of arsenate and arsenite, although As(V) predominates (IARC, 2009).

As the inorganic arsenic species found most frequently in the environment, As(III) and As(V) were considered as candidate stressors. An assessment parameter was established that oxidation state will not impact the toxicity of inorganic arsenic. This assessment parameter is based upon inorganic arsenic metabolism. In the human body, inorganic arsenic is reduced from As(V) to As(III) as the initial step in metabolism. Therefore, environmental exposure to As(V) or As(III) leads to increased levels of As(III) in the human body. Because environmental exposure to As(III) or As(V) leads to increased internal levels of As(III) in humans, it was hypothesized that oxidation state of environmental inorganic arsenic would not significantly impact health effects from exposure.

1.4.3.5 Summary of Assessment Parameters for Stressors

This section summarizes the assessment parameters outlined during stressor selection for the toxicological review. The rationales for these assessment parameters are described, as are the potential qualitative impacts of these decisions.

Assessment Parameters for Stressor	Rationale	Potential Impact on Toxicological Review
Effects of environmental exposure to arsenic are largely attributable to inorganic forms of arsenic.	Inorganic arsenic forms are generally more toxic than organic arsenic compounds; inorganic compounds are more prevalent in exposure routes of concern, and inorganic arsenic is a risk driver for Agency partners and public stakeholders.	Overestimation of inorganic arsenic exposure dose due to limitations in exposure characterization (i.e., arsenic speciation) in human studies.
Oxidation state of environmental inorganic arsenic will not significantly impact health effects from exposure.	Metabolism reduces As(V) to As(III); therefore, exposure to As(V) or As(III) will lead to increased internal dose levels of As(III).	Underestimation of impact of speciation on inorganic arsenic toxicity.

1.4.4 Exposure Pathways

1.4.4.1 Summary

This section considers routes by which inorganic arsenic exposure may occur. Sources of inorganic arsenic suggest that oral, inhalation, and dermal pathways are all potential routes of exposure. An assessment parameter is established that inorganic arsenic exposure occurs through oral, inhalation, or dermal pathways, likely simultaneously. The potential impact of this assessment parameter is that limitations in inorganic arsenic exposure data may underestimate the total environmental exposure to inorganic arsenic and increase uncertainty in estimating exposure to inorganic arsenic.

1.4.4.2 Oral Exposure Pathways of Inorganic Arsenic

Oral exposure is the primary route of environmental exposure to inorganic arsenic, occurring through dietary intake of contaminated food or drinking arsenic contaminated water. Inorganic arsenic is found in meats, poultry, dairy products and cereal (IARC, 2009). In young children, oral exposure to inorganic arsenic may occur through hand-to-mouth activity with contaminated soil. Naturally occurring levels of inorganic arsenic in

soil are approximately 5 mg/kg, but can range from 1 mg/kg to 40 mg/kg depending upon the geological formation. In addition, certain foods grown in soil containing inorganic arsenic have been shown to concentrate arsenic. For the general population within the United States, the hypothesized primary route of exposure is dietary intake.

Surface water generally contains less than 10 µg/L of arsenic; however, concentrations can vary depending upon proximity to anthropogenic or natural sources of arsenic. Levels of inorganic arsenic in water can exceed 1,000 µg/L in regions with arsenic-rich geological formations. For populations living in these regions, drinking groundwater or well-water contaminated with arsenic could contribute to inorganic arsenic exposure (IARC, 2009). In addition, preparation of food in water containing inorganic arsenic could also increase arsenic content of food. Exposure to high levels of inorganic arsenic in drinking water has been documented in several regions of the world, including China, Taiwan, Bangladesh, and South America. In the United States, that average inorganic arsenic content of drinking water is 2 µg/L, although 12% of water supplies from surface water in the central United States and 12% of ground water sources in the western United States exceed 20 µg/L (ATSDR, 2007).

1.4.4.3 Inhalation Exposure Pathways of Inorganic Arsenic

For the general population, inhalation of inorganic arsenic from air is not a primary route of exposure. Exposures range from 0.02-0.6 µg/day in areas without substantial inorganic arsenic emissions from anthropogenic sources. Higher levels of inhalation exposure to inorganic arsenic are observed in more "polluted" areas, and smokers can reach up to 10 µg/day of arsenic exposure (IARC, 2009; ATSDR, 2007).

Inhalation is the principal route of exposure in occupational exposure settings. Industries with potential inorganic arsenic exposure include smelting, coal-fired power plants, pressure-treated wood, glass manufacturing, and electronics industry. It is likely that ingestion and dermal exposure occurs simultaneously in certain occupational settings (IARC, 2009).

1.4.4.4 Dermal Exposure Pathways of Inorganic Arsenic

Evidence of dermal exposure to inorganic arsenic in humans is limited, although evidence in animals does suggest that dermal exposure has toxicological effects (ATSDR, 2007). Dermal exposure to inorganic arsenic has been investigated as a route of exposure in occupational settings, although these dermal exposures are most likely concurrent with inhalation and oral exposure. Although inorganic arsenic is widespread at low-levels in

the soil, it usually forms insoluble complexes with iron, aluminum, or magnesium oxide in soils surfaces which are relatively immobile and poorly absorbed in humans (ATSDR, 2007). Thus, exposure through inhalation or ingestion would likely remain predominant exposure routes.

1.4.4.5 Exposure Pathways for the Toxicological Review

For the purposes of the toxicological review, oral, inhalation, and dermal routes of exposure will be considered as contributors to environmental inorganic arsenic exposure. This assessment parameter is based upon the available exposure data as well as Agency partner and public stakeholder needs for the toxicological review.

Sources of environmental inorganic arsenic suggest that oral, inhalation, and dermal routes of exposure are all possible. Oral exposure, either through dietary exposure or drinking water exposure, is the primary source of exposure. Inhalation exposure to inorganic arsenic, either in occupational settings or in locations with high levels of arsenic emissions, likely contributes to overall exposure to inorganic arsenic. Although dermal exposure data is limited, the presence of inorganic arsenic in soils and building materials suggest that dermal exposure is likely a contributor to overall environmental arsenic exposure. In addition, Agency partners and public stakeholders have requested that oral, inhalation, and dermal routes of exposure be evaluated in the toxicological review.

1.4.4.6 Summary of Assessment Parameters for Exposure Pathways

This section of the conceptual model summarizes the assessment parameters outlined during evaluation of the exposure pathways for inorganic arsenic. The rationale for the assessment parameter is described, as is the potential qualitative impact of this decision on the hazard identification.

Assessment Parameters for Exposure Pathways	Rationale	Potential Impact on Toxicological Review
Oral, inhalation, and dermal exposure pathways all contribute to environmental inorganic arsenic exposure.	Sources of environmental inorganic arsenic indicate potential for oral, inhalation, and dermal exposure; Agency partner and public stakeholder requested all three routes of exposure be considered.	Underestimating exposure dose due to limitations in exposure characterization data based upon route of exposure which would limit dose estimation.

1.4.5 Receptors

1.4.5.1 Summary

A receptor is the population exposed to inorganic arsenic. Characterization of a receptor also includes consideration of life stages or susceptible populations that may have increased sensitivity to inorganic arsenic. This section outlines the decision to focus the toxicological review of inorganic arsenic on human health effects. With respect to susceptibility, an assessment parameter is made that considers the early life period a susceptible life stage for exposure to inorganic arsenic. The potential impact of this assessment parameter is to underestimate the health impact of subsequent inorganic arsenic exposure in individuals exposed during perinatal development.

1.4.5.2 Receptor Considerations for the Toxicological Review

Inorganic arsenic is widespread in the environment and it is possible that inorganic arsenic exposure could impact both human health and ecosystems. The toxicological review of inorganic arsenic will focus on human health impacts of inorganic arsenic exposure. This decision is based on toxicological considerations as well as Agency partner and public stakeholder needs.

Based upon the available data, humans are more sensitive to inorganic exposure than animals. Interspecies metabolism differences likely explain the differences in toxicity between animals and humans, with animals requiring higher exposure doses to reach internal doses of inorganic arsenic comparable to those observed in humans. At

environmental exposure levels of inorganic arsenic, humans are likely to be the most sensitive species. In addition, the toxicological review is expected to provide scientific support for risk management decisions. These decisions are generally based on human health impacts of chemical exposure; therefore, focusing on human health effects of inorganic arsenic exposure will ensure that the toxicological review meets Agency partner and public stakeholder needs.

1.4.5.3 Consideration of Susceptible Life Stages and Populations

Several factors may modify the association between exposure to inorganic arsenic and health outcomes among potentially susceptible populations. These factors can be considered in three broad categories: life stage, human variability, and environmental factors. Modification by life stage postulates that inorganic exposure at a particular life stage (e.g. in utero or geriatric) may have an exacerbated impact compared to exposure during other life stages. Modification due to human variability postulates that certain human populations are more sensitive to inorganic arsenic exposure. For example, such human populations may be characterized by particular socioeconomic or genetic traits which modify their response to inorganic arsenic. Environmental factors, such as diet, smoking, alcohol consumption, and exposure to mixtures, could also serve as at-risk factors by potentially exacerbating the effects of inorganic arsenic through co-exposures or epigenetic mechanisms.

Based on available health effect data on in utero exposures, the toxicological review will consider early life of human development a susceptible life stage. To identify other susceptible life stages and populations, the potential impact of life stage, human variability, and environmental factors will be evaluated using a strength of evidence framework. As shown in Table 1-4, evidence across scientific disciplines will be evaluated to examine coherence of effects and determine biological plausibility. The collective results will be used to determine if a particular factor increases effects from inorganic arsenic exposure. When data are available to identify populations or life stages potentially at increased risk to inorganic arsenic exposure, these populations or life stages will be considered.

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)

1.4.5.4 Summary of Assessment Parameters for Receptors

This section summarizes the assessment parameters described for identifying the receptor for the toxicological review. The rationales for the assessment parameters are described, as are potential qualitative impacts of these decisions.

Assessment Parameters for Receptors	Rationale	Potential Impact on Toxicological Review
The toxicological review will focus on human health effects.	Humans are more susceptible to inorganic arsenic exposure than animal species; human health effects are the driver for risk management decisions	Underestimate the impact of inorganic arsenic on ecosystems (not applicable to the toxicological review).
Populations or life stages with increased sensitivity to inorganic arsenic exposure will be considered susceptible.	Life stages, intrahuman variability, and environmental factors may exacerbate the effects of inorganic arsenic exposure.	Underestimate the impact of exposure to inorganic arsenic due to insufficient data on susceptible populations.
Early life period of human development as a susceptible life stage.	Emerging data in humans, as well as animal data, suggest that in utero exposure to inorganic arsenic may have lasting impacts.	Underestimate the health impact of subsequent inorganic arsenic exposure in individuals exposed during perinatal development.

1.4.6 Endpoints

1.4.6.1 Summary

Endpoints are measures of the effects of inorganic arsenic exposure. This section describes a causality framework for evaluating cancer and noncancer human health effects data. This section also describes several assessment parameters regarding the human relevance of health effects data. The first assessment parameter considers health effects reported in epidemiology studies relevant to humans, regardless of country of origin. This assessment parameter may result in endpoints included that may be specific to susceptible populations. A second assessment parameter states that health effects associated with inorganic arsenic exposure in epidemiological studies with no known mode of action are relevant to humans. A third assessment parameter states that health effects due to exposure to inorganic arsenic exposure in animals, in the absence of an animal-specific mode of action, are relevant to humans regardless of dose. The potential impacts of these assessment parameters are overestimating the number of health effects relevant to humans.

1.4.6.2 Evaluating Health Effects Data

The toxicological review of inorganic arsenic will consider health effects data for cancer and noncancer endpoints from subchronic and chronic exposures to inorganic arsenic. Three broad types of studies, if available, will be used to inform human health effects: controlled human exposures, epidemiologic, and toxicological studies. Controlled human exposures provide evidence of health effects following direct exposure, as well as information on the biological plausibility of associations observed in epidemiologic studies. Some study design features of controlled human exposure studies, such as small sample size and short exposure times, are limitations for estimating the effects of lifetime exposure to inorganic arsenic. In addition, controlled human exposures generally include individuals who are relatively healthy, limiting the ability to extrapolate health effects data to the general population or identify potential susceptibilities. Such study design limitations may underestimate the response to inorganic arsenic exposure.

Epidemiologic studies report associations between environmental exposure and health effects. Evaluating epidemiologic data requires consideration of several factors. The three factors most likely to impact the evaluation of epidemiologic data on inorganic arsenic are consideration of multiple chemical exposures, exposure measurement error, and effect modification. Inorganic arsenic is likely a component of multipollutant exposures in environmental exposures; therefore the contribution of inorganic arsenic to a health effect in a multipollutant exposure will be an important factor for consideration. Exposure misclassification is uncertainty associated with the measurements used to represent exposure. Epidemiologic studies often do not control chemical exposures and ecological studies often use environmental sources to estimate exposure; therefore, the impact of exposure misclassification on the health effects data for inorganic arsenic is an important consideration. Effect modification occurs when a risk modifier changes the association between exposure and health effect in different subgroups. Effect modification is an important consideration for identifying potential susceptible populations or factors impacting the observed health effects of inorganic arsenic.

In vivo toxicological studies in animals provide evidence of health effects under controlled exposure circumstances. For inorganic arsenic health effects data, a significant human database is available. Data from in vivo toxicological studies in animals will likely provide supporting evidence for human data in the toxicological review of inorganic arsenic, except when effects are only observed in in vivo toxicology studies. In such instances, the ability to extrapolate endpoints observed in animals to health outcomes in humans will be evaluated.

1.4.6.3 Role of Mechanistic Data in Hazard Identification

Mechanistic or mode of action data are informative for questions of human relevance, susceptibility, and dose-response relationships. For hazard identification, mechanistic data will be used specifically to address human relevance of the health effects data and for causal determination. Using mode of action data to inform susceptibility and dose-response relationships will be discussed in the next section of the conceptual model (Section 1.4.7 – Risk Metrics).

The toxicological review will consider health effects data from human studies and animal studies. Health effects reported in epidemiology studies will be considered relevant to humans, regardless of the country of origin. In addition, human health effects with no known mode of action will be considered relevant to humans. On the basis of these assessment parameters, evaluating mechanistic data for hazard identification is of limited value to inform the human relevance of human health effects data.

Conversely, the human relevance of in vivo toxicology data is informed by mode of action data. If health effects are reported exclusively in animal studies, mechanistic data will be used to determine human relevance of these effects. In the absence of mechanistic data indicating a mode of action not relevant to humans, health effects data from in vivo toxicology studies will be considered relevant to humans, regardless of exposure dose.

1.4.6.4 Framework for Causal Determination of Human Health Effect Endpoints

The toxicological review will assess relevant health effects data to draw conclusions on the causal relationships between inorganic arsenic exposure and human health effects. Determination of causality will focus on a range of inorganic arsenic exposure doses rather than determining causality at a specific exposure dose. The toxicological review will use a five-level hierarchy to determine causality for health effects (U.S. EPA, 2013). Table 1-5 shows the five causality descriptors for health effects and outlines the weight of evidence considerations for each descriptor. Weight of evidence evaluation will involve evaluation and integration of health effects data, as well as characterization of evidence upon which causal determination is based. This characterization will identify any data gaps which would inform future causal determinations for inorganic arsenic. Determination of causality for health effects corresponds with cancer descriptors for carcinogenic effects (U.S. EPA, 2005); therefore, this causal determination framework will be used for both cancer and noncancer health effects associated with inorganic arsenic exposure.

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.

1.4.6.5 Summary of Assessment Parameters for Endpoints

This section summarizes the assessment parameters outlined for evaluating endpoints. The rationales for the assessment parameters are described, as are the potential qualitative impacts of these decisions.

Assessment Parameters for Endpoints	Rationale	Potential Impact on Toxicological Review
Health effects data in human studies are relevant to humans, regardless of country of origin.	All available health effects data are considered for hazard identification and causal determination. Issues of susceptibility are addressed in the dose-response analysis.	Effects observed in susceptible populations considered relevant to the general population for hazard identification.
Human health effects with no known mode of action are relevant to humans.	Emerging health effects data may lack the mechanistic data, but may be important to human health. Human health effects are considered relevant in the absence of mode of action information.	Consideration of emerging health endpoints or health endpoints with limited mechanistic data in the hazard identification.
In the absence of mode of action data indicating otherwise, endpoints from animal studies are relevant to humans regardless of administered dose.	Animal studies, through study design advantages, may indicate effects at particular life stages or provide insight into progression of health effects. Animal data may be important for hazard identification and dose-response.	Consideration of emerging health endpoints which may have limited data in human populations. Species extrapolation will depend upon available scientific data (e.g., dosimetry data).

1.4.7 Risk Metrics

1.4.7.1 Summary

Risk metrics are the measure by which risk is quantified. Although risk characterization is beyond the scope of the toxicological review of inorganic arsenic, this section describes how endpoints will be selected for dose-response analysis, as well as the role of

mechanistic data for susceptibility and dose extrapolation. The issues of dose extrapolation and susceptibility will be informed using an adverse outcome pathway framework.

1.4.7.2 Selection of Endpoints for Dose-response

Health effect endpoints for which inorganic arsenic exposure is "causal" or "likely causal" will be included in the dose-response analysis (see Table 1-5). Health effect endpoints which have a "suggestive," "inadequate," or "not likely" causal relationship will not be considered for dose-response analysis.

1.4.7.3 Role of Mechanistic Data in Dose-Response Analysis: Adverse Outcome Pathway Framework

Agency partners and public stakeholders recommended evaluating the health effects of inorganic arsenic exposure using an adverse outcome pathway framework. An adverse outcome pathway connects a molecular initiating event to an endpoint at a biological level of organization. The advantage of an adverse outcome pathway is that mechanistic data are organized to answer questions in support of risk assessment decisions. However, mechanistic data or adverse outcome pathways will not be a requirement for evaluating observed health effects due to exposure to inorganic arsenic.

In the dose-response analysis of the toxicological review of inorganic arsenic, the adverse outcome pathway will address two considerations. The first consideration is uncertainty in the dose-response analysis. An adverse outcome pathway can identify where data gaps increase uncertainty in the dose-response analyses. The second consideration is variability. Human variability in response to chemical exposure may be due to various factors that affect an individual's or subpopulation's susceptibility (e.g., nutritional status). The adverse outcome pathway can inform how sources of variability (i.e. susceptibility factors) in the mode of action may impact dose-response. For instance, an adverse outcome pathway may identify molecular initiating events to which certain human populations may show additional sensitivity.

Adverse outcome pathways for the toxicological review will be developed, if possible, for causal or likely causal health effect outcomes (see Figure 1-2). Effects in this figure are examples and more effects may be attributed to inorganic arsenic. Pathways may also involve more steps. There are two important considerations for the adverse outcome pathway analysis. First, as outlined in the endpoints section, a health effect with no known mode of action is assumed to be relevant to humans. Therefore, human health

toxicity values would still be derived even in the absence of data on molecular initiating events. Secondly, regulatory decisions of Agency partners and public stakeholders are partially based upon the observation of health effects from inorganic arsenic exposure.

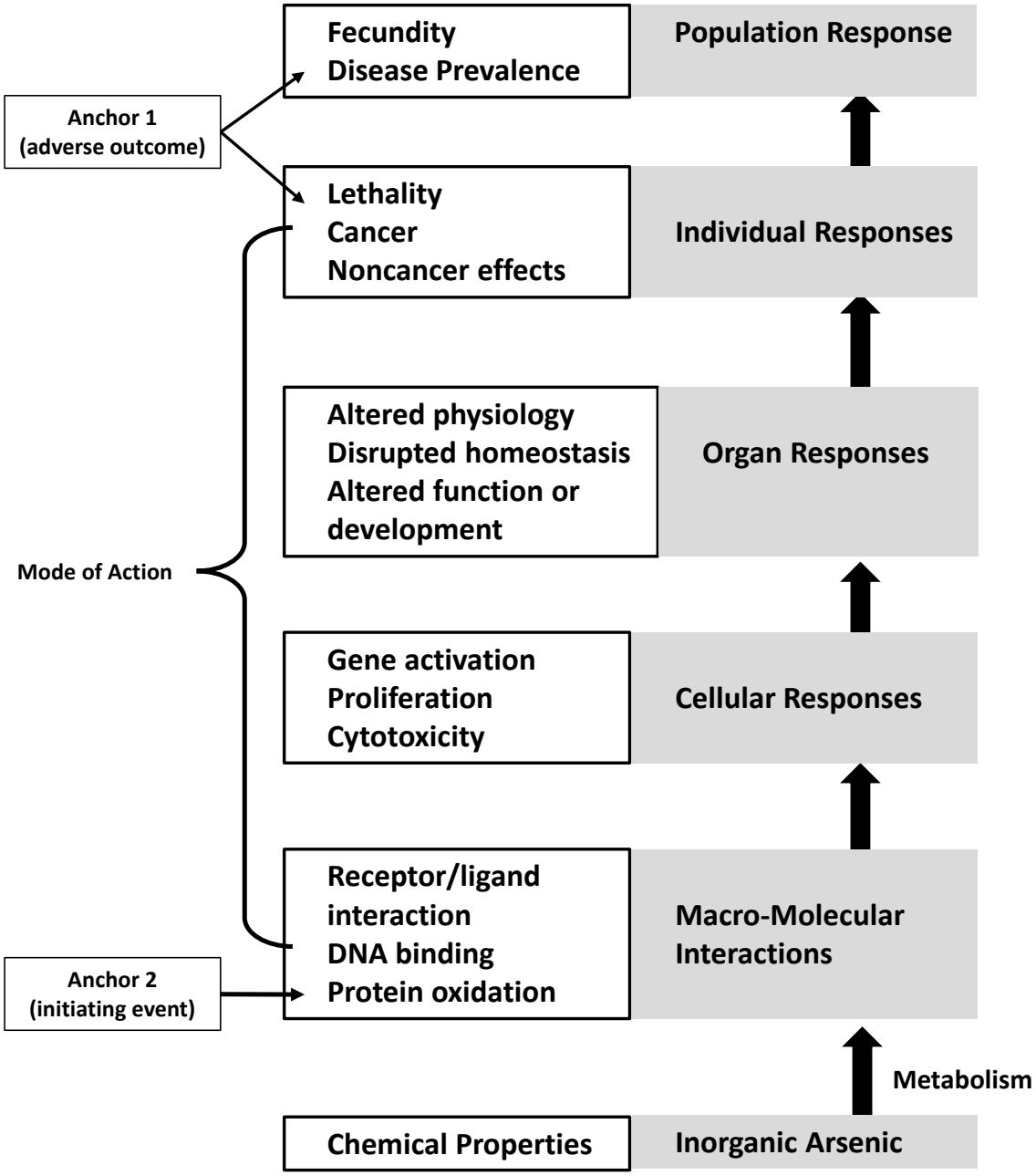


Figure 1-2 General framework for Adverse Outcome Pathway Analyses for Inorganic Arsenic

1.4.7.4 Consideration of Exposure Dose: Total Arsenic versus Inorganic Arsenic

Exposure misclassification should be considered when evaluating epidemiological studies for dose-response analyses. Ecological studies often lack individual exposure data, instead reporting human exposure using environmental sources. These environmental sources are often estimates of "total arsenic" exposure, a mixture of organic and inorganic forms of arsenic. In addition, ecological exposure metrics are often single measurements, further increasing the challenge of estimating exposure dose.

For the purposes of the toxicological review, total arsenic exposure will be considered exposure to inorganic arsenic unless exposure data are available to delineate between inorganic arsenic and total arsenic. This assessment parameter is based on two factors: the geography within which "highly" exposed populations reside and the source of inorganic arsenic exposure. Most of the ecological exposure data comes from populations living in arsenic-rich geographical regions. Generally, in populations with high levels of arsenic exposure, the primary route of exposure is consuming arsenic contaminated well water. Because the primary form of arsenic in ground water from arsenic-rich geographical regions is inorganic arsenic, it is hypothesized that the majority of intake is inorganic arsenic. The potential impact of this assessment parameter is underestimation of inorganic arsenic toxicity, as the level of inorganic arsenic in the source exposure is likely less than the reported levels of "total arsenic."

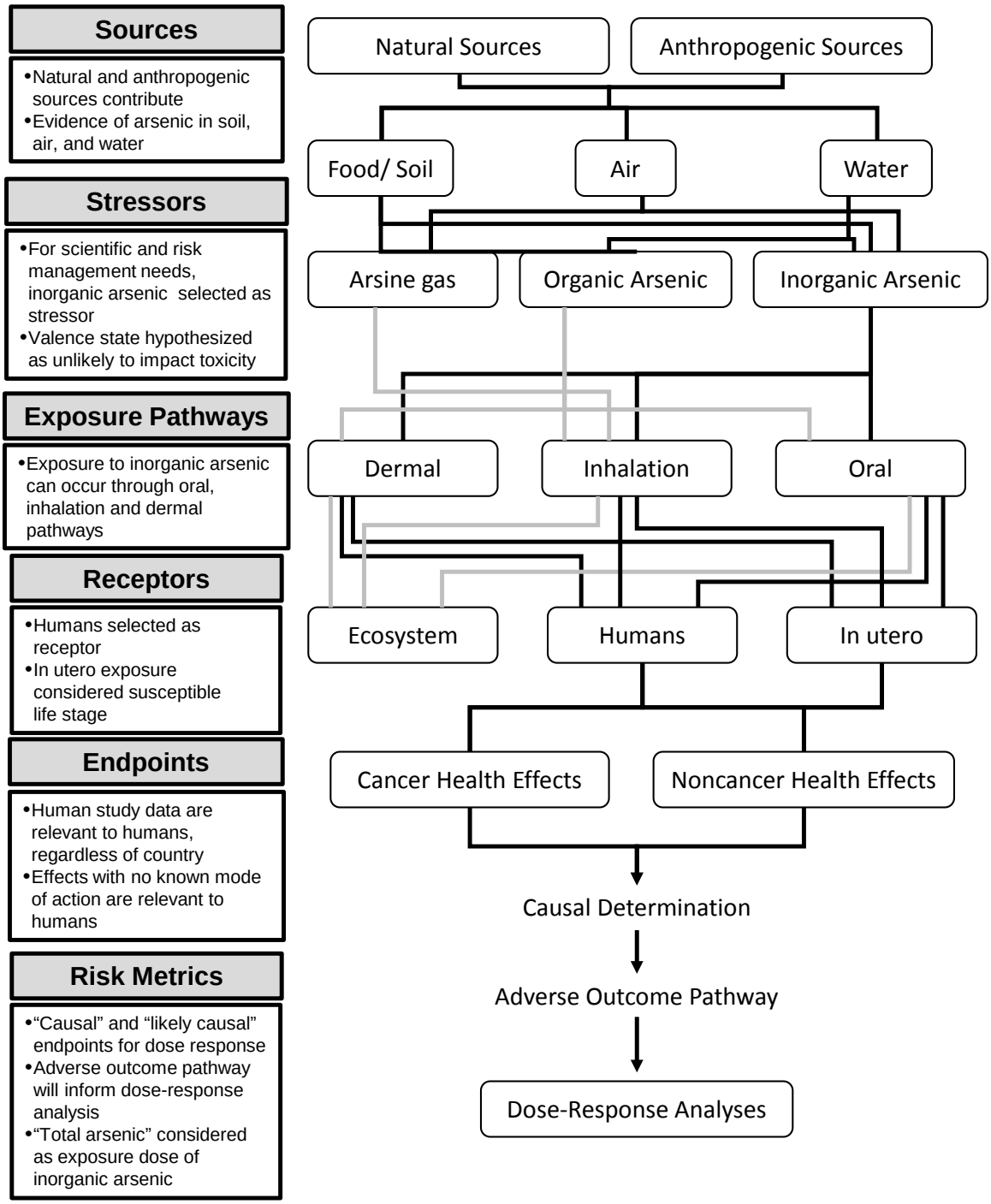
1.4.7.5 Summary of Assessment Parameters for Risk Metrics

This section summarizes the assessment parameters discussed for dose-response analyses. Rationales for assessment parameters are described, as are potential qualitative impacts of these decisions.

Assessment Parameters for Risk Metrics	Rationale	Potential Impact on Toxicological Review
For ecological studies, total arsenic will be considered exposure to inorganic arsenic.	Populations studied usually reside in arsenic-rich geographical regions and consume arsenic in drinking water; inorganic arsenic is the primary form of arsenic in well-water from arsenic-rich geography.	Underestimation of inorganic arsenic toxicity, as inorganic arsenic concentration is likely less than total arsenic level.

1.4.8 Overall Conceptual Model

Based upon the assessment parameters outlined in these sections, the overall conceptual model for the toxicological review is presented in Figure 1-3. Black lines indicate relationships that will be considered in the toxicological review, whereas gray lines indicate aspects of inorganic arsenic exposure that are beyond the scope of the toxicological review. This conceptual model may be revised based on as scientific data become available or based on recommendations from Agency partners and public stakeholders.



Source: Adapted from NRC (2009)

Figure 1-3 Overall Conceptual Model for Toxicological Review of Inorganic Arsenic

1.5 Analysis Plan for the Toxicological Review

This analysis plan is the implementation plan for developing the toxicological review of inorganic arsenic. The analysis plan expands on the conceptual model framework, describing approaches for evaluating the relationships outlined in the conceptual model.

Key Points - Analysis Plan

- The analysis plan is the implementation plan for the toxicological review
- Describes approaches to evaluate the relationships outlined in the conceptual model
- Flexible framework that can be modified during development of the toxicological review
- Revised in response to NRC recommendations in the interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic"

Like the conceptual model, the analysis 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). The analysis plan provides proposed EPA responses to NRC recommendations. When a NRC recommendation may impact multiple sections of the analysis plan, the proposed EPA responses are provided in all of the relevant sections of the analysis plan. The analysis plan can be further modified as data become available, if novel relationships become apparent during data analysis, and to implement advances in human health assessment methodology.

1.5.1 Approaches to Source Considerations

An exposure assessment is beyond the scope of the toxicological review. For the purposes of the toxicological review, inorganic arsenic will be considered widely distributed throughout the environment; specific natural or anthropogenic sources of inorganic arsenic in soil, air, or water will not be considered. Aspects of source characterization, however, are important considerations for estimating exposure to inorganic arsenic. For the purpose of estimating total daily exposure, the NRC report (NRC, 2013) indicates that delineation of exposure sources (e.g., drinking water, diet, etc.) should be characterized, preferably utilizing probabilistic approaches.

In response to the NRC recommendation, EPA will evaluate in a qualitative and, where possible, quantitative manner relationships between exposure source and biomarkers of exposure. The EPA evaluations will focus on delineating exposures to inorganic arsenic versus other forms (e.g., MMA, DMA,), with emphasis on characterizing the contribution

of specific foods (e.g., rice, fruit juices). Where possible a range of estimates regarding the contribution of unique sources of inorganic arsenic based upon an average background exposure should be evaluated as well as identification of where the lack of scientific information exists (i.e., data gaps). All studies conducted in the United States population and other populations (e.g., Taiwan, Bangladesh, etc.) will be evaluated for hazard identification and a determination may be made as to whether or not an adjustment is warranted in estimating potency in the United States population. Additionally, the available scientific information should be characterized for the bioavailability of inorganic arsenic in various media (e.g., soil, water, foodstuffs, etc.).

1.5.1.1 Supplementary Materials Related to Source Considerations

Supplementary materials for source consideration will be source characterization summary reports. These reports will characterize, based upon available data, the range of background exposures to inorganic arsenic. Background exposures to inorganic arsenic shall include all potential sources of exposure to inorganic arsenic, including but not limited to dietary, inhalation, oral, and dermal exposures. The source characterization summary reports shall be updated as new data become available. The data used to create source characterization summary reports shall be organized and maintained on EPA's HERO database (http://hero.epa.gov/).

Based upon NRC recommendations, the source characterization summary reports will focus on background exposures to inorganic arsenic for the United States population. If necessary, source characterization summary reports may be generated for non-United States populations, based upon available data.

1.5.2 Approaches to Stressor Considerations

For the purposes of the toxicological review, different oxidation states of inorganic arsenic will be considered to have the same biological effect. This assessment parameter is based upon the metabolism of inorganic arsenic, which reduces As(V) to As(III) in humans. Therefore, environmental exposure to As(V) or As(III) will result in increased internal concentrations of As(III). As exposure to inorganic arsenic in either oxidation state results in increased As(III), inorganic arsenic (either in the +3 or +5 oxidation state), is the principle stressor for the toxicological review.

The toxicological review shall summarize potential impact of chemical properties on the toxicological effects of inorganic arsenic exposure. Potential chemical properties could include forms of arsenic in the environment (e.g., organic or inorganic) or oxidation

states of the exposure compounds. Inorganic arsenic is metabolized to organic arsenic in the human body; therefore, health effects of inorganic arsenic exposure data will be informed by data on organic arsenic metabolites. Analysis of organic arsenic metabolite data will be used to address specific hypothesis regarding the effects of inorganic arsenic exposure. For instance, metabolite data may serve as a biomarker of exposure or inform adverse outcome pathway analyses. In addition, uncertainty with respect to the stressor (e.g., potential levels of organic arsenicals in exposure dose) will be considered qualitatively and/or quantitatively in dose-response analyses. The health effects of environmental exposure to organic arsenic compounds are beyond the scope of the toxicological review.

1.5.3 Approaches to Exposure Pathway Considerations

The toxicological review will characterize pathways of exposure to inorganic arsenic. Exposure pathways are processes by which a receptor is exposed to the stressor. For the purposes of the toxicological review, inorganic arsenic exposure will be considered as occurring through oral, inhalation, and dermal routes, and in some exposure scenarios, simultaneously. A critical aspect of exposure pathway considerations is capability to estimate exposure dose and/or internal dose based on available data. EPA will evaluate the feasibility for qualitative and quantitative analyses based upon the available data and physiologically based pharmacokinetic (PBPK) models. In the absence of exposure data for particular exposure route, the contribution of the route of exposure will be considered as naturally occurring levels of inorganic arsenic. For instance, if exposure data are available for dermal and oral exposure only, then inhalation exposure would be estimated at naturally occurring levels of inorganic arsenic.

Another important aspect of exposure pathway consideration is exposure misclassification. Studies may 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. Studies may report arsenic exposure concentrations from a particular source (e.g., community water supply) rather than individual exposure levels. Furthermore, these source concentrations may be estimated from samples taken over a limited period of time and extrapolated to lifetime exposures. Therefore, studies with exposure data on individuals are hypothesized to introduce less uncertainty into associations between health effect and inorganic arsenic.

1.5.3.1 Supplementary Materials Related to Exposure Pathways

Supplementary materials for exposure pathway considerations will include (1) a survey of available PBPK and/or toxicokinetic models for inorganic arsenic, (2) evaluate the applicability of PBPK models to estimate biomarkers of exposures such as inorganic arsenic and/or its metabolites levels in urine, (3) use PBPK 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 (4) feasibility study for modifying adult mouse PBPK model for developmental exposures to inorganic arsenic.

The survey of available PBPK models for inorganic arsenic will be used to determine the capability for qualitatively or quantitatively estimating exposure dose and/or internal dose based on available epidemiological data. Similarly, a reverse dosimetry model using internal biomarker concentrations would inform estimates of exposure misclassification from available drinking water exposure data.

The NRC, as well as Agency partners and public stakeholders, indicated that an important consideration for the toxicological review is developmental exposure to inorganic arsenic. In response to these recommendations, EPA shall perform a feasibility study on modifying an adult mouse PBPK model (Gentry et al., 2004) for inorganic arsenic for developmental exposure. This model shall estimate inorganic arsenic and its metabolites levels in prenatal and postnatal tissues in mice. Depending on availability of literature data, a scale up developmental PBPK model will also be considered for a humans. This study will determine (1) availability of human or animal physiological parameters and data for developing fetus and preweened offspring, (2) possibility of inorganic arsenic transport and metabolism in placental and fetal tissues, (3) availability of information to estimate metabolic and transport kinetics in placental and fetal tissues if needed, (4) availability of data and information on exposure and toxicokinetics of inorganic arsenic in lactating pups. Based on this feasibility study, EPA will develop a summary of the added value for constructing a mouse developmental exposure PBPK model to inform the health assessment of inorganic arsenic, including the arguments for and against construction of the developmental PBPK model for mice and humans.

1.5.4 Approaches to Receptor Considerations

Receptors are populations, including life stages, which are exposed to the stressor. For the purposes of the toxicological review, the receptor selected was humans. Potential

human receptors include the general population and populations that may be at increased risk to inorganic arsenic exposure because of certain factors (e.g., diet, pre-existing diseases, smoking, alcohol consumption, exposure to mixtures, and life stages). The toxicological review will evaluate human populations and life stages for susceptibility using a strength of evidence framework. This framework evaluates data across scientific disciplines to determine if a factor results in a population or life stage being at increased risk of exposure to inorganic arsenic.

A reference population is necessary for comparisons to susceptible populations. The reference population for the toxicological review will be the United States population. As part of characterizing the reference population, EPA will examine potential associations between drinking water exposure and health effect endpoints (e.g., mortality, bladder cancer, cardiovascular disease, diabetes) in the United States. There are potential impacts for selecting as a reference receptor the United States population. The United States standard of living, including access to health care and ability to relocate from environmental sources of exposure, could also lead to a healthier population with fewer health effects relative to other countries or nationalities. In addition, the United States population consists of several ethnic groups, which may limit the ability to determine the impact of genetic susceptibility or ethnicity on health effects from inorganic arsenic exposure.

Identification of susceptible life stages requires comparison of effects with a reference life stage. Life stages will be categorized, where possible, on the basis of biological development rather than age ranges. The reference life stage for the toxicological review will be sexually mature adults. The toxicological review will consider early-life as a susceptible life stage in humans.

Receptor considerations are also important for dose-response analyses. Factors, such as smoking, life stage, or underlying disease, may increase susceptibility relative to the reference population. EPA will develop sensitivity analyses to determine how receptor considerations impact dose-response analyses for inorganic arsenic.

1.5.4.1 Supplementary Materials Related to Receptors

Supplementary materials for receptor considerations will include (1) receptor evidence tables, (2) receptor sensitivity analyses, and (3) an analysis of potential associations between drinking water exposure to inorganic arsenic exposure and health effect endpoints. The data used to create these supplementary materials will be available on EPA's HERO database (http://hero.epa.gov/).

Receptor evidence tables will summarize the available evidence considered during evaluation of potential receptors for the IRIS toxicological review of inorganic arsenic. At a minimum, these tables will include the relevant bibliographic information, description of study design/quality, reported effects of inorganic arsenic exposure, and dose-response information. These tables will be updated as new data become available.

Receptor sensitivity analyses will inform how receptor considerations impact dose-response analyses for inorganic arsenic. Receptor considerations for sensitivity analyses will include, but are not limited to, smoking synergism size effect for health effects associated with inorganic arsenic.

Analyses examining the potential associations between drinking water exposure and health effect endpoints in the United States will also be provided as supplementary material. Endpoints may include, but are not limited to, mortality, bladder cancer, cardiovascular disease, and diabetes. These data will inform comparisons of susceptible populations with the general population of the United States.

1.5.5 Approaches to Endpoint Considerations

Endpoints are measures of the health effects of exposure to inorganic arsenic. Potential endpoints associated with exposure to inorganic arsenic to be considered in this toxicological review include both cancer and noncancer health effects.

The endpoint evaluation process for inorganic arsenic includes multiple steps. The first step is identification of available literature relevant for hazard identification. After identifying the relevant literature, risk of bias (internal validity) evaluations will be performed using the draft approach developed by the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) (NTP, 2013). Studies and risk of bias evaluations will inform strength of evidence determinations on the causal relationships between inorganic arsenic exposure and particular health effects. Based upon the causal determinations, particular health endpoints will be considered for dose-response analysis (see Section 1.5.6 – Approaches to Risk Metric Considerations).

1.5.5.1 Approaches to Endpoint Considerations – Identifying Relevant Literature

EPA is committed to evaluating the available literature on inorganic arsenic by incorporating elements of systematic review. Systematic review is a scientific investigation of a specific question that uses explicit, pre-specified methods to identify, select, summarize, and assess relevant study findings. For the literature search, this

involves an iterative process for identifying and selecting relevant scientific information needed to address assessment-specific questions. The systematic review process formulates specific strategies to identify and select studies relating to each question, evaluates study methods based on clearly defined criteria, and transparently documents the process and its outcomes.

The initial literature search process for the toxicological review of inorganic arsenic includes: selecting databases of references, defining search terms, documenting search strategies, and a strategy for periodically updating the literature search. In addition, public submissions of relevant studies will be considered during development of the toxicological review. These literature search products will be publicly available through HERO (http://hero.epa.gov/). The end product of this initial literature search process is a comprehensive list of the available scientific literature on inorganic arsenic.

Figure 1-4 outlines the overall literature search strategy for the toxicological review. Searches will be conducted using the HERO interface and periodically updated. Databases will be searched using the appropriate forms of the chemical name and CAS number to "cast a wide net." The main databases that will be used in the literature search are PubMed, Web of Science, and Toxline. Duplication records will be removed. The gray lines in Figure 1-4 indicate literature which were removed from the literature search process, whereas the dark lines indicate literature which will be considered during development of the toxicological review.

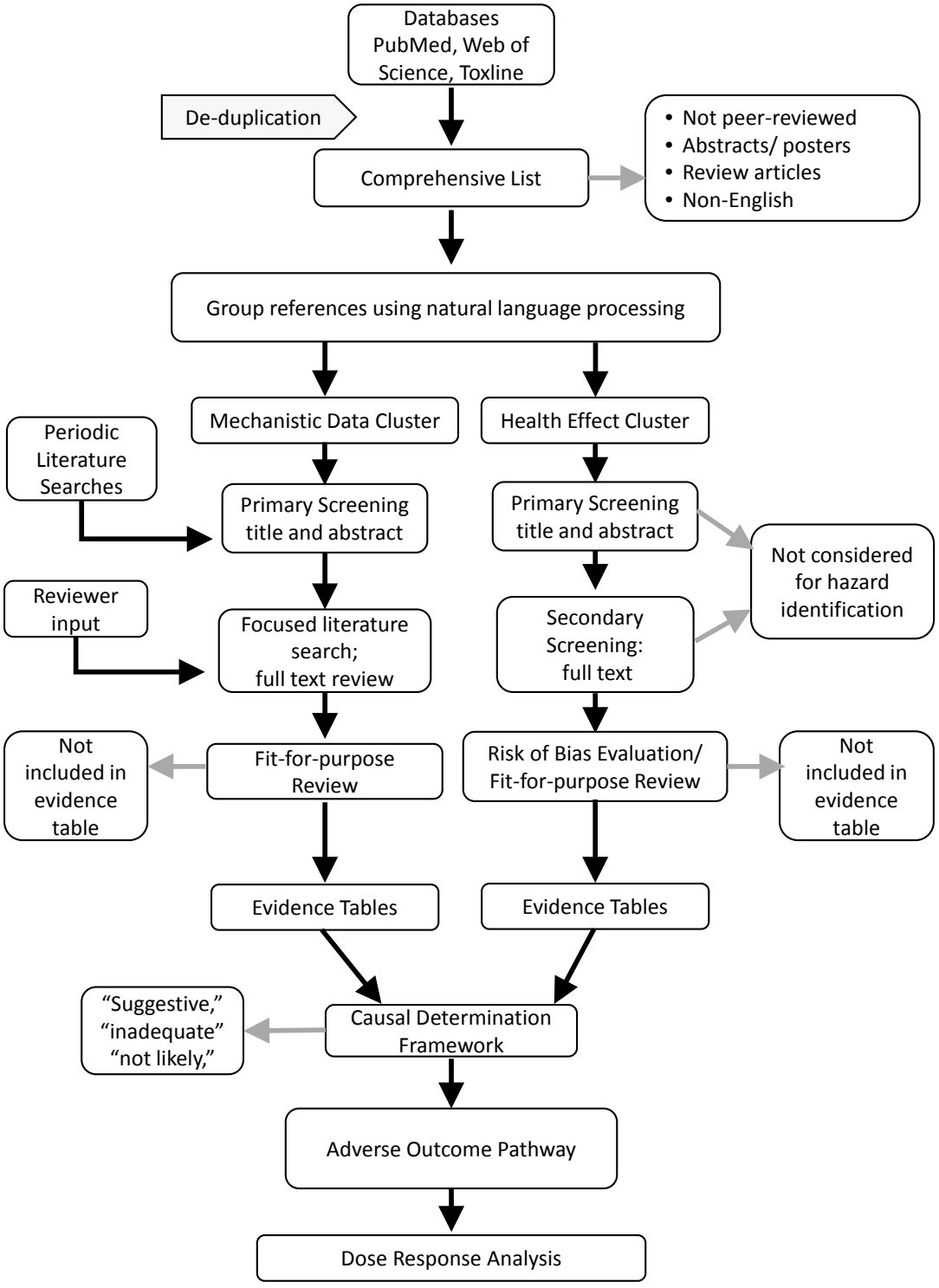


Figure 1-4 Overall Process for Identifying Studies for the Toxicological Review

From the comprehensive list of references identified by this literature search strategy, non-peer reviewed articles, abstracts and posters, review articles, and non-English references will be removed from the initial screening. Review articles will be considered in the development of the toxicological review; however, the toxicological review generally evaluates data from primary source material. The remaining references in the considered list will be grouped using natural language processing. A computer algorithm groups references into "clusters" based on similarity in the title and abstract. The clustering process is a tool to organize the arsenic literature database; it is not an exclusion step.

References in these clusters will undergo primary screening by title and abstract. The purpose of the primary screening is to categorize studies, it does not exclude studies from consideration. Studies in other categories will be considered, as needed, to address other questions such as toxicokinetics, mode of action, or susceptibility. The categories for the primary screening of the health effect cluster are shown in in the Appendix (Section 1.6, see Table 1-9).

Following categorization by title and abstract, studies were further reviewed using full text. The purpose of the full text review was to identify studies that would be relevant to hazard identification for inorganic arsenic. All epidemiologic and toxicological studies identified as likely to contain information supporting hazard identification based on title and abstract review were further characterized to identify characteristics of the study design and the health effects reported in the study. Based upon the full text review, epidemiologic and animal toxicology studies considered relevant to hazard identification were selected for risk of bias evaluations.

The literature search for arsenic will be periodically updated. The references identified in the updated literature search will bypass the natural language processing step and enter into primary screening. Similarly, references recommended by Agency partners, public stakeholders, or reviewers will undergo secondary screening, bypassing both natural language processing and primary screening. All of the screening processes will be captured in a publicly available database.

1.5.5.2 **Approaches to Endpoint Considerations – Evaluating Risk of Bias**

Following primary literature screening, studies will be evaluated for potential risk of bias. These risk of bias evaluations are not exclusion criteria, rather, the evaluations will determine the primary literature considered for hazard identification. Although studies with a relatively high risk of bias will not be presented in evidence tables, these studies may be considered supporting evidence for hazard identification. The magnitude and the

direction of the bias will be evaluated in order to consider the coherence of findings from these supporting studies, within the context of the full body of evidence.

Risk of bias will be evaluated using a modified draft OHAT approach (NTP, 2013). The draft OHAT approach identifies studies and extracts data from all of the available studies, regardless of potential risk of bias. After data extraction, a series of questions addressing selection bias, performance bias, attrition/exclusion bias, detection bias, and selective reporting bias are applied to each study (Table 1-6). Individual studies are assessed for risk of bias on an outcome basis using a 4-point scale (definitely low bias, probably low bias, probably high bias, and definitely high bias). In the next step of the OHAT approach, confidence ratings are developed that the group of studies on a particular outcome reflect the true relationship between exposure to substance and that outcome. Confidence ratings consider study design, factors that decrease confidence (such as risk of bias or indirectness) and factors that increase confidence such as evidence of dose-response or consistency across animal species. These confidence ratings are translated into evidence of health effects and integrated to develop hazard identification conclusions.

The toxicological review for inorganic arsenic will evaluate risk of bias using a modification of the OHAT approach. These modifications are necessary because of the different types of questions addressed in evidence-based medicine compared to a toxicological review. For evidence-based medicine, the question addressed is typically narrowly focused in scope, resulting in a smaller literature database for evaluation. In contrast, the scope of an IRIS toxicological review is much broader, addressing potential toxicity in multiple tissue types across a broad dose range for various populations. As a result, the relevant literature database for an IRIS toxicological review of inorganic arsenic is much larger. Effective use of resources to develop a toxicological review incorporating systematic review methods requires modifications to the draft OHAT approach. The draft OHAT approach was modified such that potential risk of bias was determined before extracting data from the studies.

Table 1-6 Example Risk of Bias Considerations

Category	Risk of Bias Questions*
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)?

*Note, in consultation with OHAT, questions number 7, 9 and 15 were restated from the 2013 draft (NTP, 2013) so that answering "yes" would consistently indicate lower risk of bias, while answering "no" would indicate higher risk of bias.

Analysis of risk of bias necessarily requires subjective conclusions by an expert scientist. Thus, to ensure consistency across the evaluators, OHAT drafted guidance for each risk of bias question to ensure the ratings are applied as objectively and transparently as possible. Each risk of bias question is assigned one of four standard ratings, ranging from *definitely low* risk of bias to *definitely high* risk of bias (see Table 1-7). The evaluation of each question depends on the availability of evidence of biased practices.

Table 1-7 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, generally from the study report or through contacting the authors) (May include specific examples of relevant low risk of bias practices)
(+) *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 (May include specific examples of relevant high risk of bias practices)

1.5.5.2.1 Risk of Bias Evaluation Criteria for Epidemiologic Studies

For evaluation of the inorganic arsenic literature, each study will be independently evaluated by two scientists who refer to the OHAT Guidance for Assessing Risk of Bias - Appendix 2 (NTP, 2013). After independently reviewing a given study, the two reviewers discuss differences and resolve discrepancies between their ratings.

As a starting point, case-control, cohort, and cross-sectional studies were evaluated. Other study types, such as ecological studies, provide less direct support for causal determinations because individual-level exposure information is not used in the analyses. Ecological studies are not excluded from consideration in the overall causal determination for a given health outcome and will be used to provide further support in making causal inferences when other types of studies are not available. Some ecological studies are expected to provide supporting information regarding exposure during sensitive development times (e.g., in utero or childhood exposures) or exposure to susceptible populations. The Appendix (Section 1-6, see Table 1-10) provides additional information used in evaluating risk of bias for inorganic arsenic. The table provides criteria for the risk of bias standard ratings for each OHAT question considered.

1.5.5.2.2 Risk of Bias Evaluation Criteria for Animal Toxicology Studies

For evaluation of the inorganic arsenic literature, each study will be independently evaluated by two scientists who refer to the OHAT Guidance for Assessing Risk of Bias - Appendix 2 (NTP, 2013). After independently reviewing a given study, the two reviewers discuss differences and resolve discrepancies between their ratings. The Appendix (Section 1-6, see Table 1-11) provides additional information used in evaluating risk of bias for inorganic arsenic. The table provides criteria for the risk of bias standard ratings for each OHAT question considered.

1.5.5.3 Approaches to Endpoint Considerations – Impact of Risk of Bias on Hazard Identification

Risk of bias evaluations will not be used to exclude studies from consideration. Rather, the risk of bias evaluations will be used to tier studies based on the risk of bias ratings for the individual questions. Data from studies with low risk of bias ratings on many elements will be considered "low risk of bias studies," whereas data from studies with high risk of bias on many elements will be considered "high risk of bias studies." Although "high risk of bias" studies will not have data extracted, these studies will be considered supporting evidence for hazard identification. Data with "low risk of bias" will be extracted and considered principal evidence for hazard identification.

Risk of bias determinations will be made using a modified version of the draft OHAT approach (NTP, 2013). In the modified OHAT approach, individual studies will be evaluated using a series of questions. Each question will be scored using a 4- point scale (definitely low bias, probably low bias, probably high bias, and definitely high bias), such that each individual study will have a rating for each of the 15 risk of bias questions. The modified OHAT approach will not produce an "overall" risk of bias rating for each study. The evaluation strategy for setting tiers will be unique depending upon the available database; however, all epidemiologic studies can be evaluated using a single strategy because the same risk of bias questions are applied across all studies. Similarly, all animal toxicology studies can be evaluated using a single strategy.

1.5.5.3.1 Risk of Bias Tiering for Epidemiologic Studies

The evaluation strategy for tiering epidemiologic studies based on risk of bias outlined here is specific for inorganic arsenic. The evaluation strategy for inorganic arsenic is intended to be inclusive; therefore, the evaluation strategy for tiering studies based on

risk of bias will focus on four elements or risk of bias questions. These four components will be:

- confidence in the observed association based on a study design allowing for evaluation of association between exposure and outcome
- confidence in the exposure characterization
- confidence in the outcome assessment
- confidence that there were no other threats to internal validity of the study

Of the 15 risk of bias questions evaluated, six were selected as most informative to address potential risk of bias of the available data. The six questions that will be used for tiering epidemiologic studies based on the risk of bias are shown below in Table 1-8. Based upon the risk of bias ratings for these questions, data will be considered either "low risk of bias" and used for hazard identification or "high risk of bias" and used to support hazard identification conclusions. Potential scenarios for responses to the six questions located in column 1 result in a determination for risk of bias in the last row (Tiering data) of Table 1-8.

Table 1-8 Determining data tiers using risk of bias evaluations

OHAT Risk of Bias Questions	**Risk of bias ratings**							
Were the comparison groups appropriate? (*Confidence in observed association*)	**++** or **+**	Any of the six questions is a **- -**	Any	Two of the three questions are **–**	**–**	Three of the other four questions are **–**	No more than one of the other five questions is a **–**	**++** or **+**
Did the study design or analysis account for important confounding and modifying variables? (*Confidence in observed association*)	**++** or **+**	Any of the six questions is a **- -**	Any	Two of the three questions are **–**	**–**	Three of the other four questions are **–**	No more than one of the other five questions is **–**	**++** or **+**

OHAT Risk of Bias Questions	**Risk of bias ratings**							
Did researchers adjust or control for other exposures that are anticipated to bias results? (*Confidence in observed association*)	**++** or **+**	Any of the six questions is a **- -**	Any	Two of the three questions are **–**	**–**	Three of the other four questions are **–**	No more than one of the other five questions is **–**	++ or +
Can we be confident in the exposure characterization? (*Confidence in exposure characterization*)	**++** or **+**	Any of the six questions is a **- -**	**–**	**++** or **+**	**–**	**–**	**–**	**–**
Can we be confident in the outcome assessment? (*Confidence in outcome assessment*)	**++** or **+**	Any of the six questions is a **- -**	**–**	**++** or **+**	**–**	**++** or **+**	No more than one of the other five questions is **–**	**++** or **+**
Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)? (Other Threats to *Internal Validity*)	**++** or **+**	Any of the six questions is a **- -**	**–**	**–**	Any	Three of the other four questions are **–**	No more than one of the other five questions is **–**	**++** or **+**

OHAT Risk of Bias Questions	**Risk of bias ratings**							
Additional considerations							If one of those questions is unintended exposure and the study is an occupational setting, then study would be further considered for data extraction. If exposure characterization received a – because the study did not measure arsenic then low risk of bias	If exposure characterization received a – because the study did not measure arsenic then the study would be further considered for data extraction.
Tiering data	Low risk of bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	Low risk of bias	Low risk of bias

1.5.5.3.2 Risk of Bias Tiering for Animal Toxicology Studies

The evaluation strategy for tiering animal toxicology studies based on risk of bias outlined here is specific for inorganic arsenic. The evaluation strategy for inorganic arsenic is intended to be inclusive; therefore, the evaluation strategy for tiering studies based on risk of bias will focus on two elements of risk of bias questions. These two components will be:

- confidence in the exposure characterization
- confidence in the outcome assessment

Of the 15 risk of bias questions evaluated, two were selected as most helpful to address potential risk of bias in the available data. The two risk of bias questions that will be used for tiering studies based on the risk of bias are Question 12 and Question 13 (see Table 1-7). Based upon the risk of bias ratings for these questions, data will be considered either "low risk of bias" and used for hazard identification or "high risk of bias" and used

to support hazard identification conclusions. The following decision criteria were used to distinguish studies based upon risk of bias for the animal toxicology data:

- Studies receiving ratings of either *definitely* or *probably low risk of bias* (i.e., + or ++) for Question 13 ***and also*** receiving the same ratings (i.e., + or ++) for at least half of the remaining questions were included as primary evidence for a given health effect.
- Studies receiving ratings of either *definitely* or *probably high risk of bias* (i.e., – or - -) for Question 13 ***and also*** receiving ratings of either *definitely* or *probably high risk of bias* (i.e., – or - -) for at least half of the remaining questions were judged to pose a high potential risk of bias. These studies were set aside to be reviewed after all other literature.
- Any studies receiving a rating of *definitely high risk of bias* (i.e., - -) for Question 12 were set aside for additional review.
- Studies that did not meet any of the above criteria were identified to be included as supporting evidence for a given health effect.

All animal studies identified as primary evidence for hazard identification based on the risk of bias evaluation were included in the evidence tables for arsenic.

1.5.5.4 Approaches to Endpoint Considerations – Study Evaluation

Risk of bias evaluations will be used to assess internal validity or how credible are the study findings based on study design and conduct. Risk of bias ratings will also be used to tier studies for use later in the evaluation. Individual studies are considered within the context of the full body of evidence for hazard identification, with more weight given to stronger studies with relatively low risk of bias. Studies with high risk of bias ratings on many questions will be considered "high risk of bias" studies and may be used to support findings from studies with relatively low risk of bias, but will not have data extracted. Studies with low risk of bias ratings will be considered "low risk of bias" studies and considered the principal data for hazard identification. Data from low risk of bias studies will be extracted and presented in evidence tables. Evidence tables will present data from studies related to a specific outcome or endpoint of toxicity. At a minimum, these evidence tables will include the relevant information for comparing key features such as study design, exposure metrics, and dose-response information.

Evidence tables will serve as an additional method for presenting and evaluating whether the data are fit-for-purpose (i.e., informing hazard identification for inorganic arsenic). For each health effect domain, a series of specific questions or criteria will be developed to help inform the fit-for-purpose, based upon NRC recommendations (NRC, 2013). Criteria specific for each health effect domain are needed because experimental design considerations or data analysis techniques may have a greater impact on a particular

health effect domain. For instance, a litter design may be important for developmental toxicity studies, but not as important for chronic bioassays. In addition, these specific criteria may focus the hazard evaluation to particular dose ranges or populations for particular health effects.

The criteria for these endpoint-specific evaluations will be described for each individual health effect in the hazard identification syntheses. Although, EPA is proposing to modify the OHAT approach (NTP, 2013) by evaluating fit-for-purpose after the risk of bias evaluation, because the use of endpoint or outcome specific criteria is considered critical for fit-for-purpose evaluations. The hazard identification syntheses shall evaluate the available data on individual endpoints associated with exposure to inorganic arsenic, including data presented in evidence tables. Where possible, meta-analyses for hazard identification will be performed and discussed in these synthesis sections.

1.5.5.5 Approaches to Endpoint Considerations – Causal Determination for Hazard Identification

The hazard identification syntheses will draw conclusions on the relationship between inorganic arsenic exposure and individual human health effects, using a causality framework. Causality will be determined across a range of inorganic arsenic exposures using a five-level hierarchy (see Table 1-5). The weight of evidence evaluation will be based on the evaluation and integration of health effects, along with the characterization of evidence upon which the causal determination is based. Aspects of an association that suggest causality are drawn from Hill (1965), elaborated by Rothman and Greenland (1998), and referred to in other risk assessment documents (IOM, 2008; IARC, 2006; U.S. EPA, 2005; HHS, 2004). These aspects are described below. Recommendations from the upcoming NRC IRIS review to evaluate evidence will be also be considered.

Greater strength of association lends greater confidence that the association is not due to chance or bias. Strength encompasses not only magnitude of the association, but statistical confidence in effect measure estimates. Higher precision, as reflected by narrow confidence bounds or smaller standard errors, also adds confidence in the observed association.

Consistency of the association across studies is another important consideration for causal determination. Observing an association in different study types, study populations, and exposure scenarios makes it less likely that the association is due to confounding or other factors specific to a given study, or is confined to a specific susceptible population. Characterizations of consistency should distinguish between heterogeneity of findings which may be explained (e.g., due to differences in populations,

exposure measures, ranges of exposures, potential co-exposures, and other factors specific to the exposure and health outcomes under evaluation) and unexplained variability suggesting potentially spurious findings.

Specificity is established when a single cause causes a specific effect. When established, specificity may lend greater confidence in an association; however, the absence of specificity should not detract from an association. For example, many environmental exposures may have carcinogenic action, but all contribute to a single health outcome. Conversely, a single exposure may be linked to a range of health outcomes. Therefore, evaluation of specificity should be considered in context with other criteria when determining causal relationships.

Temporality is necessary for an association to be causal. The exposure must precede the health outcome. In terms of epidemiologic studies, temporality is often cited as a main weakness of cross-sectional study designs. However, in evaluating a body of evidence, other study designs which do inform temporality can lend strength to the group of studies as a whole.

The exposure-response relationship is another aspect which lends confidence to an observed association. Observing incremental changes in the risk of a health outcome which correspond to incremental changes in the exposure of interest is an argument against a spurious association. In evaluating a body of epidemiologic studies, it may be that any one study only includes a portion of the range of exposure. Piecing together evidence from multiple studies may yield a fuller understanding of the response and the shape of the exposure-response curve over the full range of exposures. Similarly, an observed lack of response in any one study does not imply a lack of an association between exposure and a health outcome.

Biologic plausibility, coherence and analogy are addressed when weighing the totality of evidence including human, animal and mode of action. Generally, the association between exposure and a health outcome should be consistent with known scientific principles or other existing information from epidemiology, toxicology, clinical medicine, or other disciplines. A difficulty in applying these aspects is the reliance on current information, or the ‘state of the science’. Associations in the epidemiologic literature may be observed well in advance of experiments being performed or insight into mechanism or mode of action, but confidence that an association exists is strengthened by these aspects.

The final aspect is the existence of natural experiments, occurring when environmental conditions change in such a way as to mimic a controlled experiment or randomized trial, such as a change which reduces exposure. When change in exposure is followed by

changes in the risk of a health outcome of interest, this result provides greater confidence that an association exists.

In evaluating epidemiologic studies, consideration of many study design factors and issues must be taken into account to properly inform their interpretation and determine whether observed associations are likely to represent the truth or if there are reasonable alternative explanations (e.g. biases or other threats to internal validity). Such alternative explanations include "reverse causality" where the health outcome precedes exposures, chance, bias (selection bias and information bias) and confounding. These alternatives are considered in the evaluation of the aspects of causality and of the evidence as a whole.

Temporality is an essential aspect of causality and ensures that "reverse causation" is unlikely. Chance can always be a potential explanation for the results in any collection of studies but is less likely as more studies are accrued that have similar observations across different settings, study designs and populations. Selection bias may occur when study groups (e.g., exposed and unexposed, cases and controls) are not sufficiently comparable. Selection bias may alter epidemiologic findings when participation or follow-up rates are related to the probability of exposure and to the outcome of interest. Selection bias can lead to either an overestimate or underestimate of risk, and the potential direction and size of the bias must be considered when deciding whether individual studies are given more weight or less weight for a hazard evaluation. Studies where selection bias is less of a concern are typically given more weight.

The potential effects of measurement error can lead to information bias. One example is the uncertainty associated with using surrogate exposure metrics to represent the actual exposure of an individual or population. This exposure measurement error can be an important contributor to variability in epidemiologic study results. Exposure measurement error can lead to misclassification that under- or over-estimates epidemiologic associations between exposures and health outcomes, distort exposure-response relationships and widen confidence intervals around effect estimates (i.e. decrease precision). There are several components that contribute to exposure measurement error in epidemiologic studies, including the difference between true and measured concentrations and the use of average population exposure rather than individual exposure estimates. The importance of exposure misclassification varies with study design and is dependent on the spatial and temporal aspects of the available data. For a given set of epidemiologic studies informing a hazard evaluation, results from studies with more accurate exposure estimates (minimizing exposure misclassification) are given more weight, barring other serious design limitations (e.g., selection bias). Generally, exposure misclassification, when nondifferential, results in a bias toward the

null and is a potential explanation for relatively small effect estimates or for variability in results across studies with different degrees of exposure misclassification.

Confounding is a type of bias in which the apparent effect of the exposure is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (Rothman and Greenland, 1998). Scientific judgment is needed to evaluate the likely sources and extent of confounding, together with consideration of how well study designs, results, and analyses address potential confounders. The ability to statistically adjust for confounding in an epidemiologic study is dependent on the ability to identify and measure potential confounders. Consistency in reported effect estimates across multiple studies, conducted in various settings using different populations or exposures, can increase confidence that unmeasured confounding is an unlikely alternative explanation for the observed associations. Such consistency also reduces the likelihood of chance as an alternative explanation through the accumulation of a larger body of similar evidence. The observations of exposure-response trends across different studies similarly reduce the likelihood that chance, confounding, or other biases can explain the observed association. Studies in which confounding is a minimal concern are typically given more weight.

Although these aspects provide a framework for assessing the evidence, they should not be considered as a simple formula of evidence leading to conclusions about causality (Hill, 1965). In particular, not meeting one or more of the aspects does not automatically preclude a determination of causality. Rather, these aspects are taken into account with the goal of producing an objective appraisal of the evidence, which includes weighing alternative explanations. Scientific judgment is needed to evaluate individual studies and to weigh the overall body of evidence.

1.5.5.6 Approaches to Endpoint Considerations – Evaluation of Toxicological and Mode of Action Information for Hazard Identification

A causal determination for hazard identification may be based entirely on human evidence; however, evidence from animal and mode of action studies can influence the causal determination. Therefore, toxicological and mechanistic data will be considered for hazard identification.

Animal studies for hazard identification will be identified by screening the health effect cluster from the comprehensive literature search product, as well as by primary screening of the literature search updates. Toxicological data will be evaluated using the modified approach for risk of bias based upon the draft OHAT approach [(NTP, 2013); see Section 5.5.2]. Similar to the epidemiologic studies, risk of bias evaluations will not be used to

exclude studies, rather, these evaluations will be used to inform risk of bias and to tier studies based on risk of bias. Those studies with high risk of bias for multiple elements will be considered supporting evidence and studies with low risk of bias will be considered the principal data for hazard identification. Toxicological data with low risk of bias will be presented for comparison with epidemiologic data in evidence tables. The evidence tables shall contain, at a minimum, relevant information for comparing key features such as study design, sample size, and dose-response information.

Mechanistic data will be identified through natural language processing based on previous human health assessments of inorganic arsenic, as well as focused literature searches. For hazard identification, human relevance will be informed by mechanistic data. Mechanistic data will be organized into a qualitative mode of action for each health endpoint. Qualitative mode of action analyses will provide sufficient detail to inform the causal determination for each health effect. Qualitative mode of action analyses will be organized based upon an adverse outcome pathway, but are not intended to inform dose-response analyses. Health effects reported in epidemiologic studies with no known mode of action will be considered relevant to humans. Similarly, if mechanistic data are insufficient to indicate a mode of action is not relevant to humans, effects observed in animal studies will be considered relevant to humans.

1.5.5.7 Supplementary Materials Related to Endpoints

Beyond the overview of the literature search product described in the toxicological review, EPA will generate additional materials during the literature search process. One of these products will be a literature search strategy document that provides additional details on the identification and evaluation of literature for hazard identification. This literature search strategy document will describe the identification of references, the use of natural language processing to group studies, and the categorization of references by title, abstract, and/or full text review.

Hazard identification summary tables will be provided as supplementary material for endpoint considerations. Hazard identification summary tables provide an overview of the types and numbers of inorganic arsenic studies available for each health effect category. Specific outcomes as reported in the studies are characterized by health effect category, and cancer and non-cancer effects are considered together in the appropriate system. These hazard identification summary tables provide a synopsis of the data considered for hazard identification in the toxicological review.

EPA will develop qualitative hypotheses summaries as a starting point for mode of action analyses. These qualitative mode of action hypotheses summaries will briefly present the

available mechanistic data for several potential modes of action of inorganic arsenic. Potential modes of action may include, but are not limited to, apoptosis and cellular proliferation, activation of reactive oxygen species, and changes in gene expression and/or regulation. In addition, tables will be prepared summarizing the available evidence considered during qualitative evaluation of potential modes of action for inorganic arsenic. These summary tables shall be updated as new data become available. The data used to create these summary tables shall be organized and maintained on EPA's HERO database (http://hero.epa.gov/).

The NRC recommended supporting the mode of action analyses for inorganic arsenic-related health effects with microarray data. Available microarray data on inorganic arsenic will be evaluated using the Systematic Omics Analysis Review (SOAR) tool (Mcconnell, 2013). The SOAR evaluation shall be used as guidance for determining if the data are appropriate for consideration in the toxicological review. Microarray evidence considered in the toxicological review will be summarized in tables. At a minimum, these tables should include the relevant bibliographic information, description of study design/quality, SOAR scores, and dose-response information. These tables shall be updated as new data become available. The data used to create these evidence tables shall be organized and maintained on EPA's HERO database (http://hero.epa.gov/).

1.5.6 Approaches to Risk Metric Considerations

Risk metrics are measures by which effects of inorganic arsenic exposure are quantified. Dose-response analyses will be developed for cancer and noncancer health endpoints for which inorganic arsenic is "causal" or "likely causal." Mechanistic information and susceptibility will be evaluated for the potential to inform dose-response analyses.

1.5.6.1 Approaches to Risk Metric Considerations – Data Selection for Dose-Response Analyses

Dose-response analyses describe how the likelihood and severity of adverse health effects are related to the amount and condition of exposure. For inorganic arsenic, dose-response analyses will be performed for health effects for which inorganic arsenic is "causal" or "likely causal." The causal determinations required risk of bias and fit-for-purpose evaluations of the available literature for hazard identification. Similarly, these evaluations will determine which data are used for dose-response analyses. These fit-for-purpose criteria will likely be dependent upon the available data for each health effect.

Generally, it is anticipated that dose-response analyses for these health effects will be performed using epidemiologic data. Animal toxicology or in vitro data will provide a mechanistic understanding and interpretation of low dose effects observed in epidemiologic studies. When possible, dose-response analyses will be performed in the range of epidemiologic observations. Therefore, studies examining low-to-moderate levels of inorganic arsenic exposure (i.e., <100 µg/L arsenic in drinking water or comparable equivalent) will be prioritized for dose-response analyses. Furthermore, studies characterizing exposure in low-to-moderate range measuring arsenic-exposure biomarkers will be given preference over studies characterizing only water exposure at moderate-to-high arsenic levels. Other factors influencing selection of studies for dose-response analyses may include number of subjects, methods of endpoint assessment, controlling for confounders, and exposure misclassification.

1.5.6.2 Approaches to Risk Metric Considerations – Variability and Uncertainty Analysis

Uncertainty and variability represent important components that have been considered to a limited extent in human health assessment. Uncertainty represents unavailable or incomplete information on a specific variable for which the impact on human health toxicity could be described in quantitative analyses if the variable was fully characterized. Variability represents the diversity or heterogeneity of a factor that can impact the response within an individual or across a population. With respect to variability, there are many factors that play a role in determining an individual's risk from exposure, including concurrent background exposures to other chemicals, and the individual's biologic 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 toxicological review of inorganic arsenic will use mechanistic data to inform the variability and uncertainty characterizations.

1.5.6.2.1 Adverse Outcome Pathway Analysis

Dose-response analyses for causal or likely causal cancer and noncancer endpoints will be informed by mechanistic information. Specifically, mechanistic information will be used to inform variability and uncertainty in the dose-response analyses. In addition, mechanistic information could inform interpretation of low dose effects of inorganic arsenic. Mechanistic information for each endpoint will be organized into adverse outcome pathways (see Figure 1-2). Adverse outcome pathways characterize existing scientific information between a molecular initiating event and an adverse outcome for

individual and population level responses. The adverse outcome pathway framework will not displace the mode of action framework defined by the Cancer Guidelines (U.S. EPA, 2005), but be inclusive of mode of action analyses.

The extent to which an adverse outcome pathway can inform dose-response analyses is dependent upon the available mechanistic data. Data may be insufficient to support an adverse outcome pathway for particular health effects. If the mode of action is unknown, the health effect will be considered relevant to humans. Mechanistic data informing adverse outcome pathways will be identified through natural language processing based on previous human health assessments of inorganic arsenic, as well as focused literature searches. These data will be sorted by health effect and organized into the levels corresponding to an adverse outcome pathway. Data gaps preventing a complete adverse outcome pathway will be considered sources of uncertainty.

1.5.6.2.2 Susceptibility Analyses

The adverse outcome pathway structure will be used to inform variability in the dose-response. An analysis of adverse outcome pathways may be useful in characterizing the potential impact of sources of variability for health effects, such as the increased risk for particular key events or adverse outcomes. One potential source of variability is susceptibility. Using an adverse outcome pathway framework, the potential impacts of individual-level factors (e.g., sex, genetic polymorphisms, nutritional status, and cigarette smoking status) and life stages (e.g., in utero and childhood) on inorganic arsenic health effects will be characterized. To qualitatively or quantitatively evaluate contributions of susceptibility to inorganic arsenic health effects, the susceptibility factors will be linked to adverse outcome pathway(s) for each health effect. Qualitatively or quantitatively, these evaluations for susceptibility will inform the selection of the most appropriate dose-response model for individual and population level responses.

1.5.6.3 Approaches to Risk Metric Considerations – Dose-response Modeling Approaches

After organizing the available mechanistic data into an adverse outcome pathway and characterizing potential susceptibilities, dose-response analyses will be performed on endpoints for which inorganic arsenic is “causal” or “likely causal.” Probabilistic methods will be incorporated into the dose-response analyses when the necessary data are available. These probabilistic approaches are meant to characterize the uncertainty and variability in the dose-response analysis, including dose estimation, model selection, and individual and population susceptibility.

The NRC and others have recommended using novel approaches that result in a probabilistic characterization of risk as a function of dose, while incorporating issues of vulnerability. The use of probabilistic approaches to incorporate information on uncertainty and variability into the derivation of human health toxicity values for cancer and non-cancer endpoints will lead to an improved use of the available scientific information as well as promotion of research to characterize these factors. The toxicological review will qualitatively and/or quantitatively consider uncertainty and variability as separate factors impacting the derivation of human health toxicity values.

Probabilistic risk assessment approaches to the dose-response analyses for inorganic arsenic will be incorporated in a tiered manner. Each tier is associated with certain assumptions, such that higher tiers relax or eliminate assumptions made in lower tiers. Approaches described in higher tiers will likely require additional sources of information to define relationships that were fixed by assumption in lower tiers. Consequently, while it may be feasible to perform Tier 1 and Tier 2 analyses for most endpoints, the extent to which a Tier 3 analysis can be performed will be highly dependent on the availability of data for factors that impact inter-individual variability.

1.5.6.3.1 Tier 3 Probabilistic Dose-response Analyses – Inter-Individual Variability

In this tier, inter-individual level variability will be characterized when data are available. This approach will evaluate if it is possible to approximate to variability in background parameters via a probability density function, using standard sources of population-level risk data (e.g., CDC disease rate tables, NHANES data, etc.). These analyses will also examine means of integrating distributions of model predictions associated with such an analysis (derived from the distributions of background parameters) with the model-predicted distribution of estimates. For example, through Monte Carlo simulation one might be able to synthesize the variability associated with within-model uncertainty, across-model uncertainty, and inter-individual variability. These analyses may also be used to inform the impacts of susceptibility factors or other co-chemical exposures on the dose-response for inorganic arsenic.

1.5.6.3.2 Tier 2 Probabilistic Dose-response Analyses – Inter-Model and Inter-Study Uncertainty

The first phase of this tier will involve the implementation of approaches to better characterize between-model uncertainty for data from a given study.

A weighted model-averaging analysis will be implemented similar to the approach described by Wheeler and Bailer (2009). Model weights will be assigned based on individual model fit statistics obtained from the Tier 1 analysis (e.g., Akaike or Bayesian Information Criteria) and biological considerations (e.g., with respect to the likelihood of a flattening at either the low or high end of the dose-response). Sensitivity analyses will be performed to determine the impact of weight assignments and comparisons will be made with individual model results to assess the extent model averaging can reduce uncertainties in the predictions, even for extrapolated levels of interest. Nonparametric approaches will be implemented where possible and Bootstrap-based methods will be applied to the averaged estimates to provide a more-complete characterization of the uncertainty in the risk or dose estimates obtained from the model averaging approach. The product of this Tier 2 analysis will consist of probability distributions for all the estimates of interest, whether from a single model or a model average aggregate. The use of different models will illustrate the magnitude of the impact of model selection (NRC, 2013).

To address inter-study uncertainty, when the data are available, meta-analyses of study-specific results will be conducted. A non-parametric (spline-based) analysis will be completed and parametric analyses employing the relative risk models from the bootstrapping and model averaging approaches will also be examined. The goal of that examination, using maximum likelihood approaches, will be to further evaluate the relative merits of those models for risk predictions (especially at extrapolated levels), as well as to evaluate assumptions about population-to-population variability in model parameter values (e.g., background rates, and whether they differ).

1.5.6.3.3 Tier 1 Probabilistic Dose-response Analyses – Within-model uncertainty

Tier 1 consists of fitting a suite of dose-response relative risk models, selecting the best model in accordance with EPA standard BMD guidance (U.S. EPA, 2012), and making life-table-based predictions of risk. This tier evaluates within-model variability and represents the baseline probabilistic risk assessment approach. Study selection will be focused to facilitate the dose-response analyses, and preference may be given to studies with low-to-moderate exposure levels. To the extent possible, dose or exposure uncertainty will be incorporated via Monte Carlo analysis. One aspect of uncertainty relates to the likelihood that doses derived from drinking water alone do not represent the total inorganic arsenic dose. Consideration will be given to the possibility that background exposure differ across study populations. A consistent exposure metric will be required in order to allow comparisons across studies.

Relative risk models will be run on the datasets available. The analysis will generate summaries with respect to model predictions for points of departure (PODs). Consideration will be given to PODs both within and below the range of observations (dovetailing with the Tier 2 analyses described above).

1.5.6.4 Approaches to Risk Metric Considerations - Extrapolation

In previous efforts, extrapolations performed for quantitative dose-response analyses have been controversial. This controversy was recognized in the NRC interim report "Critical Aspects of EPA's IRIS Assessment of Inorganic arsenic" (NRC, 2013). To move the protection of public health beyond debates about the shape of the dose-response curve, the NRC recommended using observed data to characterize dose-response relationships. The NRC recommended limited extrapolation 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. Further, the NRC recommended characterizing dose-response relationships down to background levels, which the NRC estimated background concentrations of as 1-5 µg/L inorganic arsenic in urine for the United States populations. The NRC indicated that the risks posed by background concentrations should be characterized to the extent feasible, but that needs of assessing health risks should be facilitated by characterizing the risk down to background concentrations. Extrapolations in the toxicological review of inorganic arsenic will be informed by these recommendations.

1.6 Appendix of Materials for Evaluating Literature

This appendix provides additional details for the identification of literature as well as the evaluation of risk of bias for epidemiologic and toxicology studies. For additional information, details on the approaches to screening and evaluating the literature, please refer to Section 1.5 – Analysis Plan for the Toxicological Review of Inorganic arsenic.

Table 1-9 Categories for Primary Literature Screening

Primary Screening Category	Study Characteristics
Hazard identification	Human studies relevant for hazard identification of chronic exposure to inorganic arsenic including meta analyses; animal studies relevant for hazard identification of chronic exposure to inorganic arsenic.
Episodic exposure/acute exposure	Poisonings or short-term exposures (up to 30 days) unlikely to inform chronic health effects of inorganic arsenic exposure. This category also included case reports and case series as well as medical uses of arsenic. In some of the case series, exposure could be longer than acute or short term, but such studies are categorized here because they are supportive of the health effects of inorganic arsenic but may not be as informative for the hazard identification. If the hazard identification requires further justification, studies in this category can be reviewed at a later date if necessary.
Physical Chemistry/Engineering	Studies that examine the chemical properties of arsenic or use arsenic for chemical engineering.
Exposure Assessment	**S**tudies that only describe the sources/dose of arsenic in the air, water, food, particulate matter, plant/animal life (including feed used for livestock that humans consume), and other media. This includes bioavailability studies for the different media and studies that measured levels in humans (e.g., in nails, urine, blood) but did not evaluate any type of health effect in association with the measurements.
Non-arsenic	Studies that do not consider arsenic exposure or studies where arsenic was mentioned but was not the primary focus of the publication.
Non-peer reviewed	Studies that have not undergone peer review (e.g., newspaper articles, abstracts, posters, news and views, opinion papers, editorials, comments and replies to comments).
Ecology	Studies that describe the impact of arsenic on non-mammalian animal models (e.g., fish) or plant life.
Review/Risk Assessment/Guidance document	References that provide reviews of the available literature or references that used EPA guidelines to evaluate risk in a certain area based on exposure levels but did not directly evaluate health outcomes.

Primary Screening Category	Study Characteristics
Susceptibility	Studies in which health effects are evaluated based on factors other than dose (e.g., genetic polymorphisms, susceptibility due to methylation capacity or genetic markers, socio-economic factors, ethnicity). If the study also assessed the effects of inorganic arsenic before assessing the effects of the susceptibility factors, it was considered for the hazard identification.
Mode of Action	Studies that examine the molecular events occurring after inorganic arsenic exposure (e.g., in vitro models, genomics, proteomics).
PBPK/TK	Papers that examine internal dose metrics, absorption, excretion, distribution, metabolism, etc. (toxicokinetics or TK) or detailed physiologically based pharmacokinetic (PBPK) models that model inorganic arsenic kinetics in humans or animals.
Other	Additional papers that do not fit in the above categories, including: • Public health campaigns/community knowledge, • Analytical technique papers that do not include information on dose metrics or ADME, • Co-exposure studies where inorganic arsenic cannot be separated, • Effects of a different compound in reversing the health effects of arsenic, • Arsenic bioremediation or removal of arsenic from contaminated locations, • Treatment methods for arsenic-induced disease, and • Effects on bacteria that are not related to MOA/bacterial tolerance.

Table 1-10 Additional Information for Risk of Bias Determinations for Epidemiological Studies

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
1. Was administered dose or exposure level adequately randomized?	
++	**Human Controlled Trial:** There is direct evidence that subjects were allocated to any study group including controls using a method with a random component. Acceptable methods of randomization include: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, or drawing of lots (Higgins et al., 2008). Restricted randomization (e.g., blocked randomization) to ensure particular allocation ratios will be considered low risk of bias. Similarly, stratified randomization and minimization approaches that attempt to minimize imbalance between groups on important factors prognostic factors (e.g., body weight) will be considered acceptable. **Assessment-specific Clarification:** None.
+	**Human Controlled Trial:** There is indirect evidence that subjects were allocated to study groups using a method with a random component (i.e., authors state that allocation was random, without description of the method used) **OR** it is deemed that allocation without a clearly random component during the study would not appreciably bias results. For example, approaches such as biased coin or urn randomization, replacement randomization, mixed randomization, and maximal randomization may require consultation with a statistician to determine risk of bias rating (Higgins et al., 2008). **Assessment-specific Clarification:** None.
-	**Human Controlled Trial:** There is indirect evidence that subjects were allocated to study groups using a method with a non-random component **OR** there is insufficient information provided about how subjects were allocated to study groups. Non-random allocation methods may be systematic, but have the potential to allow participants or researchers to anticipate the allocation to study groups. Such "quasi-random" methods include alternation, assignment based on date of birth, case record number, or date of presentation to study (Higgins et al., 2008). **Assessment-specific Clarification:** None.
--	**Human Controlled Trial:** There is direct evidence that subjects were allocated to study groups using a non-random method including judgment of the clinician, preference of the participant, the results of a laboratory test or a series of tests, or availability of the intervention (Higgins et al., 2008). **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
2. Was allocation to study groups adequately concealed?	
++	**Human Controlled Trial:** There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable. Methods used to ensure allocation concealment include central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or equivalent methods. **Assessment-specific Clarification:** None.
+	**Human Controlled Trial:** There is indirect evidence that the research personnel and subjects did not know what study group subjects were allocated to **OR** it is deemed that lack of adequate allocation concealment would not appreciably bias results. **Assessment-specific Clarification:** None.
-	**Human Controlled Trial:** There is indirect evidence that at the time of recruitment it was possible for the research personnel and subjects to know what study group subjects were allocated to, or it is likely that they could have broken the blinding of allocation before recruitment was complete and irrevocable **OR** there is insufficient information provided about allocation to study groups. Note: Inadequate methods include using an open random allocation schedule (e.g., a list of random numbers), assignment envelopes used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaque or not sequentially numbered), alternation or rotation; date of birth; case record number; or any other explicitly unconcealed procedure. For example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed. **Assessment-specific Clarification:** None.
--	**Human Controlled Trial:** There is direct evidence that at the time of recruitment it was possible for the research personnel and subjects to know what study group subjects were allocated to, or it is likely that they could have broken the blinding of allocation before recruitment was complete and irrevocable. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
3. Were the comparison groups appropriate?	
++	**Cohort, Cross-sectional**: There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates. **Case-Control:** There is direct evidence that cases and controls were similar (e.g., recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome. Note: A study will be considered low risk of bias if baseline characteristics of groups differed but these differences were considered as potential confounding or stratification variables (see question #4). **Assessment-specific Clarification:** Comparison groups selected adequately. Study provides table of subject characteristics by exposure levels and/or by case status. Cross-sectional studies can be considered low risk of bias if a general table of subject characteristics is provided and analyses are adjusted for confounders.
+	**Cohort, Cross-sectional**: There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates **OR** differences between groups would not appreciably bias results. **Case-Control:** There is indirect evidence that cases and controls were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age), recruited within the same time frame, and controls are described as having no history of the outcome **OR** differences between cases and controls would not appreciably bias results. **Assessment-specific Clarification:** Recruitment methods stated to be similar, but no table of information or text provided on potential differences in study subjects' characteristics that could bias results, **OR** no breakdown of subject characteristics by exposure group (or by case status) to display potential differences.
-	**Cohort, Cross-sectional**: There is indirect evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had the very different participation/response rates **OR** there is insufficient information provided about the comparison group including a different rate of non-response without an explanation. **Case-Control:** There is direct evidence that controls were drawn from a very dissimilar population than cases or recruited within very different time frames **OR** there is insufficient information provided about the appropriateness of controls including rate of response reported for cases only. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
--	**Cohort, Cross-sectional**: There is direct evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had very different participation/response rates. **Case-Control:** There is direct evidence that controls were drawn from a very dissimilar population than cases or recruited within very different time frames. **Assessment-specific Clarification:** At least one known difference between the groups was not accounted for (e.g., the study authors acknowledged that the groups were different with respect to a variable that is a potential confounder ***not*** considered in the analysis), **OR r**ecruitment methods were very different (e.g., recruitment completed during different time frames, different criteria were used for recruitment).
4. Did the study design or analysis account for important confounding and modifying variables?	
++	**Human Controlled Trial, Cohort, Cross-sectional, Case Series/report:** There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, case matching, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified. Acceptable consideration of appropriate adjustment factors includes cases when the factor is not included in the final adjustment model because the author conducted analyses that indicated it did not need to be included. **Case-Control:** There is direct evidence that appropriate adjustments were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research specific bias including standardization, matching of cases and controls, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified. **Assessment-specific Clarification:** Study adjusted for or addressed important potential confounders. Age, gender, education, and socioeconomic status are potential confounders that need to be addressed and considered in the study design or analyses. In addition, specific important confounders for this assessment depend on the health outcome and include smoking for lung cancer, sun exposure for skin lesions, and alcohol drinking for hepatic outcomes. Other confounders might also be judged important for certain health outcomes. A low risk of bias rating was assigned for this question if potential confounders deemed important were adequately addressed (e.g., distribution of variables was compared between groups, and there was no statistically significant difference).
+	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report**: There is indirect evidence that appropriate adjustments were made for most primary covariates and confounders **OR** it is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results. **Assessment-specific Clarification:** Study adjusted only for some important potential confounders (e.g., sex and age), but it is likely that other confounders were present and not addressed (i.e., minimal number of confounders addressed).

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
-	**Human Controlled Trial, Cohort, Cross-sectional, Case Series/report**: There is indirect evidence that the distribution of primary covariates and known confounders differed between the groups and was not appropriately adjusted for in the final analyses **OR** there is insufficient information provided about the distribution of known confounders. **Case-Control:** There is indirect evidence that the distribution of primary covariates and known confounders differed between cases and controls and was not investigated further **OR** there is insufficient information provided about the distribution of known confounders in cases and controls. **Assessment-specific Clarification:** Design or analysis did not adjust for important potential confounders. Adjustments were made for some potential confounders, but at least one major confounder was not addressed (e.g., no adjustment for smoking when evaluating lung cancer, no adjustment for sun exposure when evaluating skin cancer).
--	**Human Controlled Trial, Cohort, Cross-sectional, Case Series/report**: There is direct evidence that the distribution of primary covariates and known confounders differed between the groups, confounding was demonstrated, and was not appropriately adjusted for in the final analyses. **Case-Control:** There is direct evidence that the distribution of primary covariates and known confounders differed between cases and controls, confounding was demonstrated, but was not appropriately adjusted for in the final analyses. **Assessment-specific Clarification:** None.
5. Did researchers adjust or control for other exposures that are anticipated to bias results?	
++	**Human Controlled Trial**: There is direct evidence that other exposures anticipated to bias results were not present or were appropriately adjusted for. **Cohort, Case- Control, Cross-sectional, Case Series/report**: There is direct evidence that other exposures anticipated to bias results were not present or were appropriately adjusted for. For occupational studies or studies of contaminated sites, other chemical exposures known to be associated with those settings were appropriately considered. **Assessment-specific Clarification:** Researchers adjusted for other chemicals or accounted for occupational exposures likely to be associated with the outcome.
+	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report**: There is indirect evidence that other co-exposures anticipated to bias results were not present or were appropriately adjusted for **OR** it is deemed that co-exposures present would not appreciably bias results. Note, as discussed above, this includes insufficient information provided on co-exposures in general population studies. **Assessment-specific Clarification:** No evidence that co-exposures were addressed as confounders, but other specific chemicals or occupational exposures were addressed.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
-	**Human Controlled Trial**: There is indirect evidence that the control group may have received the treatment or there was an unbalanced provision of additional co-exposures which were not appropriately adjusted for. **Cohort, Cross-sectional, Case Series/report**: There is indirect evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for **OR** there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated. **Case-Control:** There is indirect evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for **OR** there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated. **Assessment-specific Clarification:** There is evidence that co-exposures might not have been addressed. Examples include a study population with farmers and/or other types of workers but occupational co-exposures (e.g., to pesticides) not addressed; or a study with known co-exposures, but the relevance of the co-exposure to inorganic arsenic effects is unknown, or it is not clear if other compounds were adjusted for in the analyses.
--	**Human Controlled Trial**: There is direct evidence that the control group received the treatment or there was an unbalanced provision of additional co-exposures which were not appropriately adjusted for. **Cohort, Cross-sectional, Case Series/report**: There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. **Case-Control:** There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for. **Assessment-specific Clarification:** Known differential exposure to other chemical/pollutant also associated with the health outcome of interest occurred with inorganic arsenic, and exposure was not addressed by study authors. An example is a study of copper smelter workers where the study authors either (a) list other chemicals likely to be associated with the health outcome that the subjects were exposed to, or (b) provide levels of the other compounds, **AND** there were statistically significant differences related to the inorganic arsenic exposure that were not addressed. Such differences might have resulted from differential exposure to another compound or inorganic arsenic; thus, it cannot be determined which exposure impacted the results.
6. Were experimental conditions identical across study groups?	
NA	NA

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
7. Did researchers adhere to the study protocol?	
++	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that there were no deviations from the protocol (i.e., the study report explicitly provides this level of detail). **Assessment-specific Clarification:** None.
+	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence that there were no deviations from the protocol (i.e., authors did not report any deviations) **OR** deviations from the protocol are described and it is deemed that they would not appreciably bias results. **Assessment-specific Clarification:** Taking into consideration typical reporting practices, it seems unlikely that deviations from the protocol will be explicitly reported in most studies. Thus, unless stated otherwise by the authors (i.e., evidence of deviation is reported), or it is clear from the study report that deviations from the planned approach occurred, assume that no deviations occurred. It is anticipated that this approach will result in a rating of "probably low risk of bias" (+) for most studies. If there are deviations, the rating reflects how the deviations changed direction, magnitude and/or significance of the results.
-	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence that there were large deviations from the protocol as outlined in the methods or study report. **Assessment-specific Clarification:** None.
--	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that there were large deviations from the protocol as outlined in the methods or study report. **Assessment-specific Clarification:** None.
8. Were the research personnel and human subjects blinded to the study group during the study?	
++	**Human Controlled Trial:** There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study. Methods used to ensure blinding include central allocation, sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or equivalent methods. **Assessment-specific Clarification:** None.
+	**Human Controlled Trial:** There is indirect evidence that the research personnel and subjects were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study, **OR** it is deemed that lack of adequate blinding during the study would not appreciably bias results. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
-	**Human Controlled Trial:** There is indirect evidence that it was possible for research personnel or subjects to infer the study group, **OR** there is insufficient information provided about blinding of study group. Inadequate methods include using an open random allocation schedule (e.g., a list of random numbers), assignment envelopes used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaque or not sequentially numbered), alternation or rotation; date of birth; case record number; or any other explicitly unconcealed procedure. For example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed. **Assessment-specific Clarification:** None.
--	**Human Controlled Trial:** There is direct evidence for lack of adequate blinding of the study group including no blinding or incomplete blinding of research personnel and subjects. For some treatments, such as behavioral interventions, allocation to study groups cannot be concealed. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
9. Were outcome data complete without attrition or exclusion from analysis?	
++	**Human Controlled Trial**: There is direct evidence that there was no loss of subjects during the study and outcome data were complete **OR** loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study. Review authors should be confident that the participants included in the analysis are exactly those who were randomized into the trial. Acceptable handling of subject attrition includes: very little missing outcome data (less than 10% in each group); reasons for missing subjects unlikely to be related to outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups **OR** analyses (such as intention-to-treat analysis) in which missing data have been imputed using appropriate methods(insuring that the characteristics of subjects lost to follow up or with unavailable records are described in an identical way and are not significantly different from those of the study participants). NOTE: participants randomized but subsequently found not to be eligible need not always be considered as having missing outcome data (Higgins et al., 2008). **Cohort:** There is direct evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study. Acceptable handling of subject attrition includes: very little missing outcome data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; **OR** missing data have been imputed using appropriate methods, **AND** characteristics of subjects lost to follow up or with unavailable records are described in identical way and are not significantly different from those of the study participants. **Case-Control, Cross-sectional**: There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses. **Assessment-specific Clarification:** There are no reported data lost to attrition, and the numbers in the results tables sum to the total number of subjects, **OR** less than 10% of data are missing, **OR** there are some missing outcome data but study report clearly identifies missing data and how it was handled (e.g., loss to follow-up for a cohort study is determined to be minimal if there are some missing data for either the exposure or outcome for certain subjects at a specific time measured and the authors clearly explain what happened to everyone and which results were used in the analyses).

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
+	**Human Controlled Trial**: There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study **OR** it is deemed that the proportion lost to follow-up would not appreciably bias results (less than 20% in each group). This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records from those of the study participants. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable. **Cohort:** There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study **OR** it is deemed that the proportion lost to follow-up would not appreciably bias results. This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records from those of the study participants. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable. **Case-Control, Cross-sectional**: There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses. **Assessment-specific Clarification:** No direct evidence of loss to follow-up or attrition provided. The tables of results do not include the number of subjects and it is not stated that there was any loss data missing. There appear to be no or very few missing data, **OR i**n a cohort study, there is no mention of loss to follow-up.
-	**Human Controlled Trial**: There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large (greater than 20% in each group) and not adequately addressed **OR** there is insufficient information provided about numbers of subjects lost to follow-up. **Cohort:** There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large and not adequately addressed **OR** there is insufficient information provided about numbers of subjects lost to follow-up. **Case-Control, Cross-sectional**: There is indirect evidence that exclusion of subjects from analyses was not adequately addressed, **OR** there is insufficient information provided about why subjects were removed from the study or excluded from analyses. **Assessment-specific Clarification:** Missing outcome data with no explanation of why data was missing, and it is unclear from the characteristics table or other information provided in the report why the data might be missing.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
--	**Human Controlled Trial, Cohort:** There is direct evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large and not adequately addressed. Unacceptable handling of subject attrition includes: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation. **Case-Control, Cross-sectional**: There is direct evidence that exclusion of subjects from analyses was not adequately addressed. Unacceptable handling of subject exclusion from analyses includes: reason for exclusion likely to be related to true outcome, with either imbalance in numbers or reasons for exclusion across study groups. **Assessment-specific Clarification:** The missing outcome data are clearly related to exposure (more missing data for exposed compared to unexposed groups), but the study authors do not address why.
10. Were the outcome assessors blinded to study group or exposure level?	
++	**Human Controlled Trial**: There is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes. **Cohort, Cross-sectional, Case Series/report**: There is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes. **Case-Control:** There is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level when reporting outcomes. **Assessment-specific Clarification:** The study report states that outcome assessors were blinded to subjects' exposure levels, **OR** in a case-control study, researchers who assigned exposure levels based on drinking water level were blinded to the case/control status of the participant.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
+	**Human Controlled Trial**: There is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which may vary by outcome (i.e., blinding is especially important for subjective measures). **Cohort, Cross-sectional, Case Series/report**: There is indirect evidence that the outcome assessors were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a particular outcome). **Case-Control:** There is direct evidence that the outcome assessors were adequately blinded to the exposure level when reporting outcomes **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome or lack of blinding is unlikely to bias a particular outcome). **Assessment-specific Clarification:** No direct statement that outcome assessors were blind, but it is likely that they were (e.g., pathologists conducting histopathology on the tissue would most likely be blind to the exposure status), **OR** outcomes were assessed using an automated instrument, making it unlikely that the results would be biased since automated instrument would not be biased.
-	**Human Controlled Trial**: There is indirect evidence that it was possible for outcome assessors (including study subjects if outcomes were self-reported) to infer the study group prior to reporting outcomes, **OR** there is insufficient information provided about blinding of outcome assessors. **Cohort, Cross-sectional, Case Series/report**: There is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome) **OR** there is insufficient information provided about blinding of outcome assessors. **Case-Control:** There is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome) **OR** there is insufficient information provided about blinding of outcome assessors. **Assessment-specific Clarification:** Not enough information to determine if outcome assessors were blind to exposure status and possibility exists that they could have knowledge (e.g., it is a cohort and exposure was assessed prior to outcome), **OR l**ikely that outcome assessors were aware of exposure, but not necessarily level of exposure (e.g., outcome was assessed in subject's home, which is in either the control village or exposed village, but the study report evaluated different exposure levels in village so that when assessing the outcome, assessors would be aware that subjects were exposed or controls but not exact exposure level).

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
--	**Human Controlled Trial**: There is direct evidence for lack of adequate blinding of outcome assessors (including study subjects if outcomes were self-reported), including no blinding or incomplete blinding. **Cohort, Cross-sectional, Case Series/report**: There is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome). **Case-Control:** There is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome). **Assessment-specific Clarification:** There is direct evidence that outcome assessor knew exposure status (e.g., same situation as above with outcome assessed in the village, but the report only evaluates exposure as "exposed versus unexposed," with no arsenic levels measured).
11. Were confounding variables assessed consistently across groups using valid and reliable measures?	
++	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements. **Assessment-specific Clarification:** Methods provide specific details on how confounders were measured (e.g., for body weight, details provided to indicate precision of measurement instrument and, ideally, calibration of instrument). Validated or pretested questionnaires used.
+	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence primary covariates and confounders were assessed using valid and reliable measurements **OR** it is deemed that the measures used would not appreciably bias results (i.e., the authors justified the validity of the measures from previously published research). **Assessment-specific Clarification:** Self-administered questionnaire, **OR** questionnaire administered by a single interviewer for all subjects (thus eliminating the possibility for interviewer agreement bias), **OR** methods for assessing confounders were mixed (e.g., some methods well-conducted and consistent, but others may have been obtained from questionnaires not stated to be validated).
-	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity **OR** there is insufficient information provided about the measures used. **Assessment-specific Clarification:** Not enough details were provided on how the confounders were assessed. Questionnaire used and administered by several interviewers with no details on validity/reliability of the questionnaire or on consistency between the interviewers.
--	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that primary covariates and confounders were assessed using non valid measurements. **Assessment-specific Clarification:** There is direct evidence of selective recall by disease status.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
12. Can we be confident in the exposure characterization?	
++	**Human Controlled Trial:** There is direct or indirect evidence that the test material is confirmed as ≤ 99% pure (or impurities have been characterized and not considered to be of serious concern), and that the concentration, stability, and homogeneity of stock material and formulation have been verified as appropriate (**Note:** ≤ 99% purity value is considered achievable based on current advertised purity from Sigma-Aldrich); **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay; **AND** the study utilized spiked samples to confirm assay performance and the stability of the chemical in biological samples was appropriately addressed; **AND** studies took measures to assess potential contamination that might have occurred during sample collection and analysis, including method blanks. Note: Use of method blanks is necessary to identify potential sources of contamination in blood and urine but cannot rule out all possible sources of contamination. The risk of contamination for blood-based measurements is likely higher than for urinary measurements in part because sterile plastic blood collection containers can increase the number of sources of contamination and because of higher levels of protein and lipid levels in blood versus urine. Preferred practices include (1) measurement of the chemical for blood measurements, and (2) use of isotopically labeled dosing material (e.g., deuterated) to avoid issues of contamination, although we will not "downgrade" if a study did not follow these preferred practices. **Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay; **AND** the study utilized spiked samples to confirm assay performance and the stability of the chemical in biological samples was appropriately addressed; **AND** studies took measures to assess potential contamination that might have occurred during sample collection and analysis including method blanks. Note: Use of method blanks is necessary to identify potential sources of contamination in blood and urine but cannot rule out all possible sources of contamination. The risk of contamination for blood-based measurements is likely higher than for urinary measurements in part because sterile plastic blood collection containers can increase the number of sources of contamination and because of higher levels of protein and lipid levels in blood versus urine. Preferred practices include (1) measurement of the chemical for blood measurements, and (2) inclusion of multiple measurements of the chemical because a single sample from an individual does not appear to be strong predictor of a subject's exposure category. Use of a single measurement in large sample size studies such as NHANES is less of an issue because the number of participants offsets potential concern for differential exposure misclassification. We will not downgrade if a study did not follow these preferred practices. **Assessment-specific Clarification:** Single spot urine samples are reported for a large number of subjects (over 1,000), **OR** multiple (repeated) spot urine samples were reported. Individual-level drinking water levels (e.g., obtained from household tap or household well, but not village-level well) with methods well-described, including reporting of levels of detection (LODs). Toenail and hair samples were cleaned, **AND** the recovery rate of the method or use of internal standards is reported. More than one arsenic exposure assessment (more than one matrix, and/or more than one measurement) and at least one of them is excellent (e.g., the large HEALS cohort and spot urine spot samples, in addition to village-level water inorganic arsenic measurements) and a correlation reported between the different measurements.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
+	**Human Controlled Trial**: There is direct or indirect evidence that purity was ≤ 98%, (or impurities have been characterized and not considered to be of serious concern i.e., purity was independently confirmed by lab, purity is reported in paper or obtained through author query, or purity not reported but the source is listed and the supplier of the chemical provides documentation of the purity of the chemical; **AND FOR INTERNAL DOSIMETRY STUDIES** there is indirect evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay, i.e., the central estimate (median, mean, geometric mean) is ***above*** the LOQ but results for individual data values are not presented or the presentation of variance estimates do not permit assessment of whether most data points are likely ***above*** the LOQ; **AND** the study utilized spiked samples to confirm assay performance and the chemical in biological samples was appropriately addressed; **AND** studies took measures to assess potential contamination that might have occurred during sample collection and analysis including method blanks. **Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence that most data points for the chemical are ***above*** the LOQ for the assay, i.e., the central estimate (median, mean, geometric mean) is ***above*** the LOQ but results for individual data values are not presented or the presentation of variance estimates do not permit assessment of whether most data points are likely ***above*** the LOQ; **AND** the study utilized spiked samples to confirm assay performance and the stability of the chemical in biological samples has been appropriately addressed; **AND** studies took measures to assess potential contamination that might have occurred during sample collection and analysis including method blanks; OR use of questionnaire items where results of biomonitoring studies support the use of the questionnaire item(s) as an indicator of relative level of exposure; **OR** job description for occupational studies where levels in the work environment or results of biomonitoring studies support the use of job description as an indicator of relative level of exposure. **Assessment-specific Clarification:** Single spot urine samples with a moderate number of subjects (i.e., hundreds or more). Adequate measurements and methods, but LODs are not provided. Exposure based on occupational title but supported by some arsenic monitoring (air, urine or other biomarker).

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
-	**Human Controlled Trial**: Neither the source or purity of the chemical was reported in the study and information on purity could not be obtained through author query/vendor documentation; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct or indirect evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay **BUT** no steps were taken to assess potential contamination that might have occurred during sample collection and analysis; **OR** there is indirect or direct evidence that most individual data points for the chemical are ***below*** the level of quantitation (LOQ) for the assay; **OR** method to measure the chemical used ELISA which is less accepted as providing quantitatively accurate values and because of potential uncharacterized antibody cross-reactivity with conjugates and endogenous components of sample matrices **Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct or indirect evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay **BUT** no steps were taken to assess potential contamination that might have occurred during sample collection and analysis; **OR** there is indirect or direct evidence that most individual data points for the chemical are ***below*** the level of quantitation (LOQ) for the assay; **OR** method to measure the chemical used ELISA which leads to concern because of uncharacterized antibody cross-reactivity with conjugates and endogenous components of sample matrices; **OR** use of questionnaire items that are not supported by results of biomonitoring studies; **OR** job description for occupational studies that are not supported by information on levels in the work environment or results of biomonitoring studies **Assessment-specific Clarification:** Exposure based on single spot urine sample for a limited number of subjects (less than 100), **OR** exposure based on occupational title with no arsenic monitoring, **OR** cumulative arsenic levels based on self-reported duration/resident history and group well water measurements.
--	**Human Controlled Trial**: There is indirect or direct evidence that purity was <98%; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct evidence of uncontrolled contamination. **Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence of uncontrolled contamination; **OR** not reporting of methods used to assess exposure and this information could not be obtained through author query; **OR** self-report exposure. **Assessment-specific Clarification:** No measured arsenic concentrations. Exposure assessed based on presence/absence of skin lesions OR self-reported duration of drinking water or living in a certain area OR Lifetime cumulative arsenic exposure determined using self-reported information on residential history and drinking-water daily consumption rates, and village-level median inorganic arsenic concentration in drinking water.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
13. Can we be confident in the outcome assessment?	
++	**Human Controlled Trial, Cohort:** There is direct evidence that the outcome was assessed using well-established methods, the "gold standard" or with validity and reliability >0.70 and subjects had been followed for the same length of time in all study groups. Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries. **Case-Control:** There is direct evidence that the outcome was assessed in cases using well-established methods (the gold standard) and subjects had been followed for the same length of time in all study groups. **Cross-sectional, Case Series/report**: There is direct evidence that the outcome was assessed using well-established methods (the gold standard). **Assessment-specific Clarification:** Cancer cases are histologically confirmed, **OR** data obtained from nationwide registry are accepted as valid and complete (e.g., Taiwan), **OR** outcome diagnosed by physician, **OR** outcome obtained from medical record data or validated with such data (if self-reported).
+	**Human Controlled Trial, Cohort:** There is indirect evidence that the outcome was assessed using acceptable methods [i.e., deemed valid and reliable but not the gold standard or with validity and reliability ≤ 0.40] and subjects had been followed for the same length of time in all study groups **OR** it is deemed that the outcome assessment methods used would not appreciably bias results. Acceptable, but not ideal assessment methods will depend on the outcome, but examples of such methods may include proxy reporting of outcomes and mining of data collected for other purposes. **Case-Control:** There is indirect evidence that the outcome was assessed in cases (i.e., case definition) using acceptable methods and subjects had been followed for the same length of time in all study groups **OR** it is deemed that the outcome assessment methods used would not appreciably bias results. **Cross-sectional, Case Series/report**: There is indirect evidence that the outcome was assessed using acceptable methods **OR** it is deemed that the outcome assessment methods used would not appreciably bias results. **Assessment-specific Clarification:** Death certificates are used, but there is no statement that they were coded by certified nosologist, **OR** information on the accuracy/validity/completeness of the death certificates is missing, **OR** incident cancer cases are not stated to be histologically confirmed, but the study was conducted in a hospital setting (e.g., hospital-based case-control study).

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
-	**Human Controlled Trial, Cohort:** There is indirect evidence that the outcome assessment method is an insensitive instrument, the authors did not validate the methods used, or the length of follow up differed by study group **OR** there is insufficient information provided about validation of outcome assessment method. **Case-Control:** There is indirect evidence that the outcome was assessed in cases using an insensitive instrument or was not adequately validated **OR** there is insufficient information provided about how cases were identified. **Cross-sectional, Case Series/report**: There is indirect evidence that the outcome assessment method is an insensitive instrument or was not adequately validated **OR** there is insufficient information provided about validation of outcome assessment method. **Assessment-specific Clarification:** Outcome is self-reported (e.g., "ever been diagnosed by a physician") and not verified by medical records or other means. There is insufficient information on quality of self-report or validation of answers. Outcome is assessed by nurses and there is no information on assessor agreement.
--	**Human Controlled Trial, Cohort:** There is direct evidence that the outcome assessment method is an insensitive instrument, or the length of follow up differed by study group. **Case-Control:** There is direct evidence that the outcome was assessed in cases using an insensitive instrument. **Cross-sectional, Case Series/report**: There is direct evidence that the outcome assessment method is an insensitive instrument. **Assessment-specific Clarification:** Self-reported outcome when question is not worded "as diagnosed by a physician" and cannot be verified.
14. Were all measured outcomes reported?	
++	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction. **Assessment-specific Clarification:** None.
+	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** analyses that had not been planned at the outset of the study (i.e., retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the omitted analyses were not appropriate and selective reporting would not appreciably bias results. This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not). **Assessment-specific Clarification:** All outcomes outlined in abstract, introduction, and methods are reported.

Risk of Bias Questions and Rating Guidelines – Epidemiology Studies	
-	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** there is insufficient information provided about selective outcome reporting. **Assessment-specific Clarification:** If an outcome mentioned in a part of the study report is obviously missing from the results.
--	**Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report:** There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect). **Assessment-specific Clarification:** None.
15. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?	
	On a project specific basis, additional questions for other potential threats to internal validity can be added and applied to study designs as appropriate.
++	**Assessment-specific Clarification:** Statistical analyses were appropriate and no other threats to internal validity were identified. Study authors might acknowledge limitations, but these are not expected to affect the study's internal validity.
+	**Assessment-specific Clarification:** There are study limitations likely to bias the results towards or away from the null, but adequate sample size was available in each cell (n≤ 5), **OR** sample size is small and acknowledged as a potential limitation by study authors, but significant results were still observed.
-	**Assessment-specific Clarification:** There are study limitations likely to bias results towards or away from the null, **OR** analyses were conducted on a small number of subjects (n<5 in any given cell) and no statistically significant results were observed.
--	**Assessment-specific Clarification:** None.

Source: Adapted from NTP (2013)

Table 1-11 Additional Information for Risk of Bias Determinations for Animal Toxicology Studies

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
1. Was administered dose or exposure level adequately randomized?	
++	There is direct evidence that animals were allocated to any study group including controls using a method with a random component. Acceptable methods of randomization include: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, or drawing of lots (Higgins et al., 2008). Restricted randomization (e.g., blocked randomization) to ensure particular allocation ratios will be considered low risk of bias. Similarly, stratified randomization and minimization approaches that attempt to minimize imbalance between groups on important factors prognostic factors (e.g., body weight) will be considered acceptable. This type of approach is used by NTP and included in OECD guidelines for toxicology protocols, i.e., random number generator with body weight as a covariate such that body weight is consistent across study groups. Discrimination criteria applied prior to randomization across study groups (e.g., only female rats displaying normal estrus cycles in the prior 3 months were included; rats were then randomly assigned to study groups using a random number table) will also be considered acceptable. Investigator-selection of animals from a cage is not considered random allocation because animals may not have an equal chance of being selected, e.g., investigator selecting animals with this method may inadvertently choose healthier, easier to catch, or less aggressive animals. Use of concurrent controls is required as an indication that randomization covered all study groups. **Assessment-specific Clarification:** None.
+	There is indirect evidence that animals were allocated to study groups using a method with a random component (i.e., authors state that allocation was random, without description of the method used) **OR** it is deemed that allocation without a clearly random component during the study would not appreciably bias results. For example, approaches such as biased coin or urn randomization, replacement randomization, mixed randomization, and maximal randomization may require consultation with a statistician to determine risk-of-bias rating (Higgins et al., 2008). Use of concurrent controls is required as an indication that randomization covered all study groups. **Assessment-specific Clarification:** None.
-	There is indirect evidence that animals were allocated to study groups using a method with a non-random component **OR** there is insufficient information provided about how subjects were allocated to study groups. Non-random allocation methods may be systematic, but have the potential to allow researchers to anticipate the allocation of animals to study groups (Higgins et al., 2008). Such "quasi-random" methods include investigator-selection of animals from a cage, alternation, assignment based on shipment receipt date, date of birth, or animal number. A study reporting lack of concurrent controls is another indication that randomization to all study groups was not conducted. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
--	There is direct evidence that animals were allocated to study groups using a non-random method including judgment of the investigator, the results of a laboratory test or a series of tests (Higgins et al., 2008). A study reporting lack of concurrent controls is another indication that randomization to all study groups was not conducted. **Assessment-specific Clarification:** None.
2. Was allocation to study groups adequately concealed?	
++	There is direct evidence that at the time of assigning study groups the research personnel did not know what group animals were allocated to, and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable. Methods used to ensure allocation concealment include sequentially numbered treatment containers of identical appearance or equivalent methods. **Assessment-specific Clarification:** None.
+	There is indirect evidence that at the time of assigning study groups the research personnel did not know what group animals were allocated to **OR** it is deemed that lack of adequate allocation concealment would not appreciably bias results. **Assessment-specific Clarification:** Rarely reported; risk of bias based on information on randomization unless direct evidence provided in the study. If animals were randomized, it is expected that knowledge of the study groups would not appreciably bias the results unless the randomization method allows for bias.
-	There is indirect evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable **OR** there is insufficient information provided about allocation to study groups. **Assessment-specific Clarification:** None.
--	There is direct evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable. **Assessment-specific Clarification:** None.
3. Were the comparison groups appropriate?	
N/A	N/A – only applies to epidemiological studies.
4. Did the study design or analysis account for important confounding and modifying variables?	
++	There is direct evidence that appropriate adjustments were made for body weight, litter size in studies of offspring (especially when the outcome measure is growth-related and assessed prior to weaning) or any other relevant covariates. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
+	There is indirect evidence that appropriate adjustments were made for body weight, litter size in studies of offspring (especially when the outcome measure is growth-related and assessed prior to weaning), or any other relevant covariates **OR** it is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results. **Assessment-specific Clarification:** None.
-	There is indirect evidence that appropriate adjustments were not made for body weight, litter size in studies of offspring (especially when the outcome measure is growth-related and assessed prior to weaning), or any other relevant covariates **OR** there is insufficient information provided about analysis of relevant covariates. **Assessment-specific Clarification:** None.
--	There is direct evidence that appropriate adjustments were not made for body weight, litter size in studies of offspring (especially when the outcome measure is growth-related and assessed prior to weaning), or any other relevant covariates. **Assessment-specific Clarification:** None.
5. Did researchers adjust or control for other exposures that are anticipated to bias results?	
++	There is direct evidence that other exposures anticipated to bias results were not present or were appropriately adjusted for. For estrogenic exposures or endpoints anticipated to be affected by estrogenic or endocrine pathways, this would include if animals were fed a phytoestrogen-free or low phytoestrogen diet. **Assessment-specific Clarification:** None.
+	There is indirect evidence that other exposures anticipated to bias results were not present or were appropriately adjusted for **OR** it is deemed that co-exposures present would not appreciably bias results. **Assessment-specific Clarification:** Note that issues related to exposures to compound of interest addressed in question 12 regarding exposure characterization.
-	There is indirect evidence that the control group may have received the treatment or there was an unbalanced provision of additional co-exposures which were not appropriately adjusted for. For estrogenic exposures or endpoints anticipated to be affected by estrogenic or endocrine pathways, this would include if animals were likely fed a diet that did not minimize or eliminate phytoestrogen content (or phytoestrogen content of diet was not reported). **Assessment-specific Clarification:** None.
--	There is direct evidence that the control group received the treatment or there was an unbalanced provision of additional co-exposures which were not appropriately adjusted for. For estrogenic exposures or endpoints anticipated to be affected by estrogenic or endocrine pathways, this would include that animals were fed a diet that did not minimize or eliminate phytoestrogen content. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
6. Were experimental conditions identical across study groups?	
++	There is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail) and the same vehicle was used in control and experimental animals. **Assessment-specific Clarification:** Specific housing conditions reported and appear to be within standard protocol ranges without potential differences between groups
+	There is indirect evidence that the same vehicle was used in control and experimental animals **OR** it is deemed that the vehicle used would not appreciably bias results. As described above, identical non-treatment-related experimental conditions are assumed if authors did not report differences in housing or husbandry. **Assessment-specific Clarification:** None.
-	There is indirect evidence that the vehicle differed between control and experimental animals **OR** authors did not report the vehicle used. **Assessment-specific Clarification:** No concurrent vehicle was used, **OR** vehicle was different from that used for the treatment group, **OR** insufficient information to determine type of control used.
--	There is direct evidence from the study report that non-treatment-related experimental conditions were not comparable between study groups or control animals were untreated, or treated with a different vehicle than experimental animals. **Assessment-specific Clarification:** None.
7. Did researchers adhere to the study protocol?	
++	There is direct evidence that there were no deviations from the protocol (i.e., the study report explicitly provides this level of detail). **Assessment-specific Clarification:** None.
+	There is indirect evidence that there were no deviations from the protocol (i.e., authors did not report any deviations) **OR** deviations from the protocol are described and it is deemed that they would not appreciably bias results. **Assessment-specific Clarification:** None.
-	There is indirect evidence that there were large deviations from the protocol as outlined in the methods or study report. **Assessment-specific Clarification:** None.
--	There is direct evidence that there were large deviations from the protocol as outlined in the methods or study report. **Assessment-specific Clarification:** None.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
8. Were the research personnel and human subjects blinded to the study group during the study?	
++	There is direct or indirect evidence that the research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study. Methods used to ensure blinding include central allocation, sequentially numbered drug containers of identical appearance; sequentially numbered animal cages; or equivalent methods. **Assessment-specific Clarification:** None.
+	Blinding was not reported **OR** blinding was not possible but research personnel took steps to minimize potential bias, such as randomized necropsy order. **Assessment-specific Clarification:** None.
-	There is indirect evidence that the research personnel were not adequately blinded to study group and did not take steps to minimize potential bias. **Assessment-specific Clarification:** None.
--	There is direct evidence that the research personnel were not adequately blinded to study group and did not take steps to minimize potential bias. **Assessment-specific Clarification:** None.
9. Were outcome data complete without attrition or exclusion from analysis?	
++	There is direct evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study. Acceptable handling of attrition includes: very little missing outcome data; reasons for missing animals unlikely to be related to outcome (or for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; missing outcomes is not enough to impact the effect estimate **OR** missing data have been imputed using appropriate methods (insuring that characteristics of animals are not significantly different from animals retained in the analysis). **Assessment-specific Clarification:** None.
+	There is indirect evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study **OR** it is deemed that the proportion of animals lost would not appreciably bias results. This would include reports of no statistical differences in characteristics of animals removed from the study from those remaining in the study. **Assessment-specific Clarification:** Number of samples for each outcome reported.
-	There is indirect evidence that loss of animals was unacceptably large and not adequately addressed **OR** there is insufficient information provided about loss of animals. **Assessment-specific Clarification:** Number of animals treated not specified; number of samples not specified.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
--	There is direct evidence that loss of animals was unacceptably large and not adequately addressed. Unacceptable handling of attrition includes: reason for loss is likely to be related to true outcome, with either imbalance in numbers or reasons for loss across study groups. **Assessment-specific Clarification:** Mortality occurs in enough groups to make majority of data unusable.
10. Were the outcome assessors blinded to study group or exposure level?	
++	There is direct evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes. **Assessment-specific Clarification:** None.
+	There is indirect evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which may vary by outcome (i.e., blinding is especially important for subjective measures). For some outcomes, particularly pathology assessment, outcome assessors are not blind to study group as they require comparison to the control to appropriately judge the outcome, but additional measures such as multiple levels of independent review by trained pathologists can minimize this potential bias. **Assessment-specific Clarification:** Blinding not reported but not expected to bias the results because results obtained from analytical methods or other non-subjective means, **OR** two different individuals conducted independent analyses. Tests based on timing or counts are considered to be objective as is assessment of presence or absence of developmental malformations.
-	There is indirect evidence that it was possible for outcome assessors to infer the study group prior to reporting outcomes without sufficient quality control measures **OR** there is insufficient information provided about blinding of outcome assessors. **Assessment-specific Clarification:** Blinding not reported and method of analysis is subjective. For example, behavioral tests can be subjective if assessors not blinded or if includes subjective measures (e.g., response to tail pinch). Assessment of other developmental malformations such as degree of deformity is considered to be subjective.
--	There is direct evidence for lack of adequate blinding of outcome assessors, including no blinding or incomplete blinding without quality control measures. **Assessment-specific Clarification:** None.
11. Were confounding variables assessed consistently across groups using valid and reliable measures?	
++	There is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements. **Assessment-specific Clarification:** Methods provide specific details on how confounders measured (e.g., details regarding precision and calibration related to measurement of body weight provided). Litter size and sex considered to be observational results and assumed to be recorded accurately.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
+	There is indirect evidence primary covariates and confounders were assessed using valid and reliable measurements **OR** it is deemed that the measures used would not appreciably bias results (i.e., the authors justified the validity of the measures from previously published research). **Assessment-specific Clarification:** Methods for the confounder were not provided (e.g., body weight was measured, but details were not provided); assume confounders consistently assessed unless specifically stated otherwise, **OR** no confounders assessed and information for body weight or litter size provided in study and reported to be consistently measured.
-	There is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity **OR** there is insufficient information provided about the measures used. **Assessment-specific Clarification:** None.
--	There is direct evidence that primary covariates and confounders were assessed using non valid measurements. **Assessment-specific Clarification:** None.
N/A	**Assessment-specific Clarification:** No confounders assessed; rating not applicable.
12. Can we be confident in the exposure characterization?	
++	There is direct or indirect evidence that the test material is confirmed as ≤ 99% pure (or impurities have been characterized and not considered to be of serious concern), and that the concentration, stability, and homogeneity of stock material and formulation have been verified as appropriate (**Note:** ≤ 99% purity value is considered achievable based on current advertised purity from Sigma-Aldrich); **AND** the study provides information about consumption through measurement of the dosing medium and dose intake quantity, e.g., feed or water consumption; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay; **AND** the study utilized spiked samples to confirm assay performance and the stability of the chemical in biological samples was appropriately addressed; **AND** studies took measures to assess potential contamination that might have occurred during sample collection and analysis including method blanks. Note: Use of method blanks is necessary to identify potential sources of contamination in blood and urine but cannot rule out all possible sources of contamination. The risk of contamination for blood-based measurements is likely higher than for urinary measurements in part because sterile plastic blood collection containers can increase the number of sources of contamination and because of higher levels of protein and lipid levels in blood versus urine. Preferred practices include (1) measurement of the chemical for blood measurements, and (2) use of isotopically labeled dosing material (e.g., deuterated) is ideal to avoid issues of contamination, although we will not "downgrade" if a study did not follow these preferred practices. **Assessment-specific Clarification:** Analytical grade considered to be high purity, OR when substance administered in food or water, homogeneity, stability, and frequency of dose preparation reported; spillage of food and water only considered if specifically noted to be an issue or noted that it was not addressed.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
+	There is direct or indirect evidence that purity was ≤ 98% pure (or impurities have been characterized and not considered to be of serious concern),, i.e., purity was independently confirmed by lab, purity is reported in paper or obtained through author query, or purity not reported but the source is listed and the supplier of the chemical provides documentation of the purity of the chemical; **BUT** the study does not provide information about consumption through measurement of the dosing medium and dose intake quantity, e.g., feed or water consumption; **AND FOR INTERNAL DOSIMETRY STUDIES** there is indirect evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay, i.e., the central estimate (median, mean, geometric mean) is ***above*** the LOQ but results for individual data values are not presented or the presentation of variance estimates do not permit assessment of whether most data points are likely ***above*** the LOQ; **AND** the study utilized spiked samples to confirm assay performance and the stability of the chemical in biological samples has been appropriately addressed; **AND** studies took measures to assess potential contamination that might have occurred during sample collection and analysis including method blanks. **Assessment-specific Clarification:** Purity >95% and methods described and appropriate, OR homogeneity and/or stability not reported and there was no evidence that they were a concern, OR substance administered via water or food and study reports animals housed in groups so that individual intake cannot be estimated but individual measures (e.g., serum or tissue levels) reported.
-	Neither the source or purity of the chemical was reported in the study and information on purity could not be obtained through author query/vendor documentation; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct or indirect evidence that most data points for the chemical are ***above*** the level of quantitation (LOQ) for the assay **BUT** no steps were taken to assess potential contamination that might have occurred during sample collection and analysis; **OR** there is indirect or direct evidence that most individual data points for the chemical are ***below*** the level of quantitation (LOQ) for the assay; **OR** method to measure the chemical used ELISA which is less accepted as providing quantitatively accurate values and because of potential uncharacterized antibody cross-reactivity with conjugates and endogenous components of sample matrices **Assessment-specific Clarification:** Spillage of food and water not reported and were noted to be an issue, **OR** substance administered via water or food and study reports animals housed in groups so that individual intake cannot be estimated.
--	There is indirect or direct evidence that purity was <98%; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct evidence of uncontrolled contamination. **Assessment-specific Clarification:** Same criteria, but use a purity cutoff of <95%.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
13. Can we be confident in the outcome assessment?	
++	There is direct evidence that the outcome was assessed using well-established methods (the gold standard) assessed at the same length of time after initial exposure in all study groups. **Assessment-specific Clarification:** Study report provides specific details on outcome assessment including coefficient of variation, limits of detection, treatment of samples above or below limits of detection (e.g., values below detection imputed with specific value or samples diluted when above a certain range). Histopathology evaluation by pathologist and functional observational battery (FOB) with details reported are considered well-established, valid, and reliable methods.
+	There is indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard) assessed at the same length of time after initial exposure in all study groups **OR** it is deemed that the outcome assessment methods used would not appreciably bias results. **Assessment-specific Clarification:** Details provided to indicate methods seem reasonable for measuring outcome, OR commercial kit used for evaluation but limits of detection and treatment of samples above and below limits not provided.
-	There is indirect evidence that the outcome assessment method is an insensitive instrument, the authors did not validate the methods used, or the length of time after initial exposure differed by study group **OR** there is insufficient information provided about validation of outcome assessment method. **Assessment-specific Clarification:** Details not provided for methods, **OR** evaluation of outcome expected to be subjective, **OR** evaluation method not appropriate, **OR** steps not taken to ensure outcome or validate method.
--	There is direct evidence that the outcome assessment method is an insensitive instrument or the length of time after initial exposure differed by study group. **Assessment-specific Clarification:** None.
14. Were all measured outcomes reported?	
++	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction. **Assessment-specific Clarification:** Details provided for all outcomes either in report or supplemental materials.

Risk of Bias Questions and Rating Guidelines – Animal Toxicology Studies	
+	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** analyses that had not been planned at the outset of the study (i.e., retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the omitted analyses were not appropriate and selective reporting would not appreciably bias results. This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not). **Assessment-specific Clarification:** All outcomes reported but data not provided for all outcomes (e.g., statement that results not statistically significant without presentation of results). If histopathology conducted on numerous tissues, analysis of every organ does not need to be reported in results.
-	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** there is insufficient information provided about selective outcome reporting. **Assessment-specific Clarification:** Results for some outcomes, other than histopathology results, not reported.
--	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect). **Assessment-specific Clarification:** None.
15. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?	
++	On a project specific basis, additional questions for other potential threats to internal validity can be added and applied to study designs as appropriate. **Assessment-specific Clarification:** Evaluation of appropriateness of statistical analyses and evaluation to determine statistical power (i.e., if number of animals sufficient to detect effect) either based on guidelines or study report of observed statistically significant results.
+	
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Source: Adapted from NTP (2013)	

1.7 References for Assessment Development Plan

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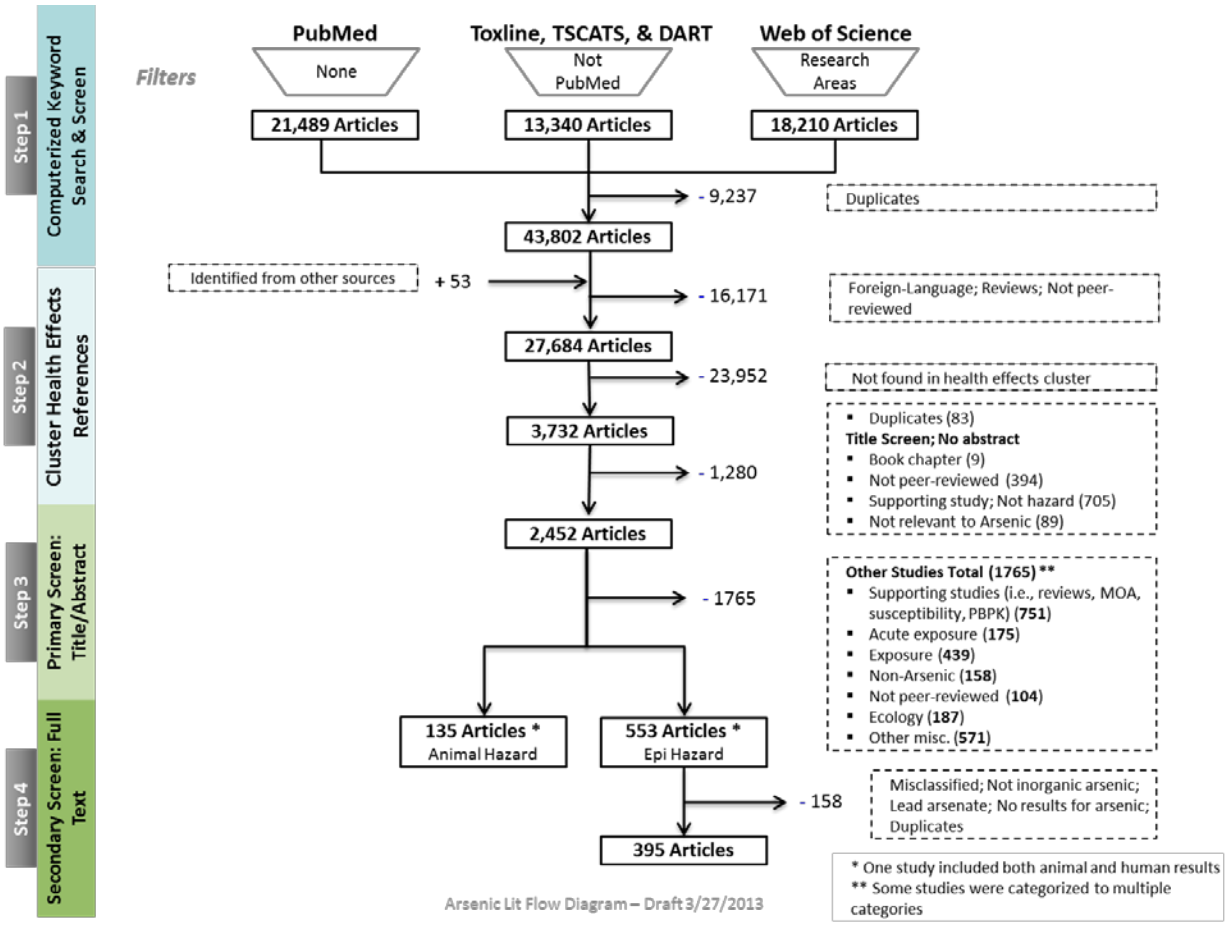
2 LITERATURE SEARCH STRATEGY AND SYSTEMATIC REVIEW FOR DEVELOPMENT OF THE TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC

2.1 Overview of Literature Search Strategy

This document describes EPA's systematic approach to literature search, screening and evaluation to identify relevant studies for the toxicological review of inorganic arsenic and summarizes the results of application of this approach. The methods that have been applied for inorganic arsenic are based on evolving EPA guidance on the IRIS process and methods for evaluating potential risk of bias proposed by the National Toxicology Program (NTP) at NIEHS. This approach includes the following components:

- **Computerized keyword search** of PubMed, Web of Science, and Toxline using search terms presented here with search updates conducted through December 2013;
- **Health effects cluster determination** using natural language processing to group studies based on the similarity of their titles and abstracts and then clustering references around known relevant "seed" studies to identify a subset for further review;
- **Categorization of references** by subject based on manual review of the title and abstract of each, thereby identifying the toxicology and epidemiology studies that support the identification of a human hazard for inorganic arsenic;
- **Characterization of studies and development of hazard identification tables** using the previously identified toxicology and epidemiology studies, resulting in an overview of the available hazard identification literature;
- **Evaluation of potential risk of bias** of studies, enabling the identification of the literature likely to serve as primary evidence; and
- **Development of evidence tables** for each health effect category that summarize the primary evidence available.

Figure 2-1 below outlines the steps in the literature search and review process leading up to development of the hazard identification tables and figures. The results of the systematic review of the inorganic arsenic literature are summarized as well, including the numbers of references identified and screened.



*Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

Figure 2-1 Literature Flow Diagram

2.2 Computerized Keyword Search

The objective of the literature search was to systematically identify and evaluate published literature to consider during development of the toxicological review. To ensure the capture of all of the scientific literature pertinent to assessing the chronic human health effects of exposure to inorganic arsenic, the initial literature search conducted in January 2013 included the PubMed, Web of Science, and Toxline databases. The search strings used for each database are provided in Table 2-1. This initial search resulted in 53,039 references, and after duplicate studies were removed (i.e., studies that appeared in the search results of multiple databases), 43,802 unique

references remained. Additional references submitted for consideration by Agency partners and public stakeholders were added to the list of potentially relevant studies. References identified as foreign-language, not peer-reviewed, or review articles were set aside

The initial literature search is updated monthly to identify new literature recently published; unique studies are added to the overall literature database. Those studies that are published in English, peer reviewed, and present original research (i.e., not review articles) are carried through the process to determine if they are relevant to the hazard identification for inorganic arsenic. The current appendices include studies identified in the literature search updates conducted through December 2013.

2.3 Health Effects Cluster Determination

The subset of unique references in hand after completion of the first step were then clustered into groups on the basis of language similarity using OmniViz reference visualization software. Using natural language processing, the titles and abstracts of the references were grouped based on similarity. To identify references relevant for hazard identification, approximately 900 references were used as "seed" references. "Seed" references are those previously identified by experts as relevant to hazard identification in peer reviewed inorganic arsenic human health risk assessments. Reference clusters containing one or more of these "seed" references were used to create the health effects cluster of 3,732 references. These 3,732 references formed the basis of subsequent screening for relevance for hazard identification.

References identified after the initial literature search were screened manually and clustering was not applied.

Table 2-1 Search Strings for Initial Literature Search

Database	Search String
PubMed	("arsenic"[MeSH Terms] OR "arsenic"[All Fields]) OR "7440-38-2"[All Fields] OR "inorganic arsenic"[All Fields] OR "monomethylarsenic"[All Fields] OR "dimethylarsenic"[All Fields] OR "methyl arsenic"[All Fields] OR "monomethylarsonic acid"[All Fields] OR (124[All Fields] AND 58[All Fields] AND 3[All Fields]) OR "monomethylarsonous acid"[All Fields] OR "dimethylarsinic acid"[All Fields] OR "75-60-5"[All Fields] OR "dimethylarsinous acid"[All Fields] OR "arsenate"[All Fields] OR (12523[All Fields] AND 21[All Fields] AND 6[All Fields]) OR "arsenite"[All Fields] OR (7784[All Fields] AND 46[All Fields] AND 5[All Fields]) OR "cacodylic acid"[All Fields] NOT "arsenic trioxide"[All Fields])
Web of Science	(TS=arsenic OR TS="7440-38-2" OR TS="inorganic arsenic" OR TS=monomethylarsenic OR TS=dimethylarsenic OR TS=methylarsenic OR TS="monomethylarsonic acid" OR TS="124-58-3" OR TS="monomethylarsonous acid" OR TS="dimethylarsinic acid" OR TS="cacodylic acid" OR TS="75-60-5" OR TS="dimethylarsenous acid" OR TS=arsenate OR TS="12523-21-6" OR TS=arsenite OR TS="7784-46-5") NOT TS="arsenic trioxide" NOT WC="Geochemistry Geophysics" NOT WC="Physics Applied" NOT WC="Physics Condensed Matter" NOT WC="Materials Science Coatings Films" NOT WC=Optics NOT WC="Chemistry Physical" NOT WC=Mechanics NOT WC="Instruments Instrumentation" NOT WC="Engineering Manufacturing" NOT WC="Materials Science Characterization Testing" NOT WC=Electrochemistry NOT WC="Metallurgy Metallurgical Engineering" NOT WC="Chemistry Analytical" NOT WC="Engineering Environmental" NOT WC="Materials Science Multidisciplinary" NOT WC="Chemistry Inorganic Nuclear" NOT WC="Engineering Electrical Electronic" NOT WC="Engineering Chemical" NOT WC=Spectroscopy NOT WC=Crystallography NOT WC="Engineering Civil" NOT WC="Nanoscience Nanotechnology" NOT WC=Mineralogy NOT WC="Physics Atomic Molecular Chemical" NOT WC="Mining Mineral Processing" NOT WC="Energy Fuels" NOT WC="Materials Science Paper Wood" NOT WC="Materials Science Ceramics" NOT WC="Materials Science Characterization Testing" NOT WC="Physics Nuclear" NOT WC="Polymer Science" NOT WC=Geology NOT WC=Limnology NOT WC="Engineering Manufacturing" NOT WC="Agricultural Engineering" NOT WC="Engineering Mechanical" NOT WC="Computer Science Hardware Architecture" NOT WC="Imaging Science Photographic Technology")
Toxline	(7440-38-2 OR 124-58-3 OR 75-60-5 OR 7784-46-5 OR arsenic OR "inorganic+arsenic" OR monomethylarsenic OR dimethylarsenic OR methylarsenic OR "monomethylarsonic acid" OR "monomethylarsonous acid" OR "dimethylarsinic acid" OR "dimethylarsinous acid" OR arsenate OR arsenite OR arsenicals) NOT "arsenic trioxide"

2.4 Categorization of References

Categorization and all steps following were performed in a database to facilitate data management, record-keeping with respect to decisions, and consistency across evaluations conducted by multiple reviewers.

2.4.1 Categorization of Health Effects Literature Based on Title and Abstract

Studies in the health effects cluster were categorized based on review of the title and abstract and placed in one or more of the following pre-determined categories. The primary purpose of this step was to identify epidemiology and toxicology studies potentially relevant to the hazard identification for inorganic arsenic. Studies in other categories might prove useful to development of other sections of the toxicological review and were set aside for later review.

Two individuals independently assigned one or more categories to each reference. In cases where the two reviewers' categorization decisions differed, a third senior reviewer evaluated the information and made the final decision. The primary screening identified 653 epidemiology studies and 99 animal studies. The full list of categories used in this step included the following study categories.

- **Epidemiologic hazard identification:** Human studies relevant for hazard identification of chronic exposure to inorganic arsenic; this included meta-analyses.
- **Animal hazard identification:** Animal studies relevant for hazard identification of chronic exposure to inorganic arsenic.
- **Episodic exposure/acute exposure:** Poisonings or short-term exposures (up to 30 days) that are supportive of the health effects of inorganic arsenic but not related to chronic health effects of inorganic arsenic exposure. This category also included case reports and case series as well as medical uses of arsenic. In some of the case series, exposure could be longer than acute or short term, but such studies are categorized here because they are supportive of the health effects of inorganic arsenic but may not be as informative for the hazard identification. If the hazard identification requires further justification, studies in this category can be reviewed at a later date if necessary.
- **Physical chemistry/engineering:** Studies that examine the chemical properties of arsenic or uses of arsenic in chemical engineering.

- **Exposure assessment:** Studies that only describe the sources/dose of arsenic in the air, water, food, particulate matter, plant/animal life (including feed used for livestock that humans consume), and other media. This includes bioavailability studies for the different media and studies that measured levels in humans (e.g., in nails, urine, blood) but did not evaluate any type of health effect in association with the measurements.
- **Non-arsenic:** Studies that do not consider arsenic exposure or studies where arsenic was mentioned but was not the primary focus of the publication.
- **Non-peer reviewed:** Studies that have not undergone peer review (e.g., newspaper articles, abstracts, posters, news and views, opinion papers, editorials, comments and replies to comments).
- **Ecology:** Studies that describe the impact of arsenic on non-mammalian animal models (e.g., fish) or plant life.
- **Review, risk assessment, or guidance document:** References that provide reviews of the available literature or references that used EPA guidelines to evaluate risk in a certain area based on exposure levels but did not directly evaluate health outcomes.
- **Susceptibility:** Studies in which health effects are evaluated based on factors other than dose (e.g., genetic polymorphisms, susceptibility due to methylation capacity or genetic markers, socio-economic factors, ethnicity). If the study also assessed the effects of inorganic arsenic before assessing the effects of the susceptibility factors, it was considered for the hazard identification.
- **Mode of action (MOA):** Studies that examine the molecular events occurring after inorganic arsenic exposure (e.g., in vitro models, genomics, proteomics, genotoxicity, reactive oxygen species).
- **PBPK/TK**: Papers that examine internal dose metrics, absorption, excretion, distribution, and metabolism (i.e., toxicokinetics, or TK) or detailed physiologically based pharmacokinetic (PBPK) models that model inorganic arsenic kinetics in humans or animals.
- **Other:** Additional papers that do not fit in the above categories, including:
  - Public health campaigns/community knowledge,
  - Analytical technique papers that do not include information on dose metrics or ADME,
  - Co-exposure studies where inorganic arsenic cannot be separated,
  - Effects of a different compound in reversing the health effects of inorganic arsenic,
  - Arsenic bioremediation or removal of arsenic from contaminated locations,
  - Treatment methods for arsenic-induced disease, and
  - Effects on bacteria that are not related to MOA/bacterial tolerance.

Studies with no abstract were evaluated separately and placed into one of the following groups:

- Book chapters;
- Not peer-reviewed, including abstracts (identified based on a single page reference), letters, comments, and editorials;
- Supporting studies;
- Not relevant to arsenic; or
- Epidemiologic or animal hazard identification (references in this group were further categorized as described below).

Duplicate references were set aside, and only one instance of the study advanced to the next round of screening.

2.4.2 Further Categorization of Epidemiologic and Animal Hazard Identification Studies

Epidemiology studies were further categorized to identify studies reporting effects associated with inorganic arsenic exposure. The evaluation of these references was also conducted by two reviewers independently, with a third individual evaluating the study when the first two reviewers differed. Studies were set aside if they reported the following types of exposures:

- Exposure to organic arsenic only;
- Exposure other than to inorganic arsenic only, including cases where the arsenic exposure could not or was not evaluated separately from other possible exposures;
- Occupational exposure where there was no evaluation of arsenic only (e.g., evaluation of effects in glass workers or copper smelter workers compared to the general population without any other qualifying exposure information);
- Environmental exposure where there was no evaluation of arsenic only;
- Studies where arsenic was not the primary focus (e.g., arsenic was only noted as a confounder for evaluating other chemical exposures); and
- Studies of exposure to arsenical pesticides or lead arsenate.

These studies might be reviewed later in the development; however, they will not serve as primary evidence for development of the hazard identification and causal determination for inorganic arsenic.

References were also reserved for review in the next step if it was not possible, based on review of the title and abstract, to determine if results were reported for exposure to inorganic arsenic only. These included:

- Studies reporting exposure to an unknown form of arsenic;
- Occupational study where arsenic was evaluated separately from other chemical exposures; and
- Environmental exposure (e.g., air or dust) where results were evaluated separately for arsenic.

In cases where only urinary or blood levels of arsenic were available, it was not always possible to identify the type of arsenic exposure based on review of title and abstract. Because inorganic arsenic is metabolized, the metabolites can be measured in the urine or blood. Studies reporting urinary or blood arsenic levels of metabolites only were categorized as "not inorganic arsenic only." Reviewers tended to err on the side of inclusion in cases where categorization was not clear based on title and abstract review, so that the full text of studies could be reviewed in the following step. However, if both reviewers selected "not inorganic arsenic only," the study was characterized as such and not further evaluated.

2.5 Characterization of Studies and Development of "Summary of Epidemiological/Toxicological studies for Hazard Identification" Tables

The full text of all epidemiology and toxicology studies identified as reporting inorganic arsenic exposure, including exposure to unknown forms of arsenic, was reviewed to determine the following characteristics.

Epidemiology Studies	Toxicology Studies
• Route of exposure • Country in which the study population lived • Study design • Health effects observed, grouped by system	• Route of exposure • Species and strain • Study design • Health effects observed, grouped by system

The information was entered into DRAGON by one reviewer, and each entry was independently checked by another reviewer.

In many studies, more than one route of exposure is possible (e.g., an occupational study can evaluate exposures via inhalation and dermal, or a study focusing on oral exposures can also have dermal components if the subjects also bathed in the water). In these cases, the primary route of exposure was used for characterization purposes. In cases where only measurements in blood or urine were available and the study did not indicate the possible exposure route (e.g., only urine levels available in subjects who live in a rural environment with no indication of potential exposure), the study was characterized as both oral and inhalation.

Health effects were categorized using a pre-determined standard vocabulary included in DRAGON. In general, health effect categories represent biological systems and health effects can be logically assigned to the appropriate system. In a few cases, the category is more general and represents a collection of outcomes that are not easily categorized in a specific system (e.g., eye effects are assigned to the "Other" group).

At any point in these characterizations, a study could be considered misclassified and assigned back to one of the original categories used *a priori* in the Primary Screen. For example, a publication might re-evaluate data previously published elsewhere. If the publication provides an independent evaluation of data, it was included as part of the hazard identification. However, if the main objective of the publication was a critique of the methods used by others and not a truly independent review (i.e., one presenting previously unpublished evaluation results), it was categorized under "review/risk assessment/guidance document" for potential use as supporting evidence.

The tables in the appendix provide an overview of the types and numbers of inorganic arsenic studies available for each health effect category. Epidemiology studies are characterized based on study design, route of exposure, country, and health effects reported. Specific outcomes as reported in the studies are characterized by health effect category, and cancer and non-cancer effects are considered together in the appropriate system. The specific health effect is included in the hazard identification tables, with cancer outcomes listed as "neoplastic lesions." When no studies of a particular type or exposure route were identified, placeholders for those study types or routes are omitted from the tables and figures.

2.6 Evaluation of Potential Risk of Bias

The next step in the evaluation process was the analysis of the risk of bias for each study. Because the literature database was still large after the initial screening, categorization,

and characterization steps, assessing risk of bias can help to further differentiate primary evidence from supporting evidence for hazard identification.

2.6.1 General Approach for Risk of Bias Evaluation

The Office of Health Assessment and Translation (OHAT) at the National Institute of Environmental Health Science (NIEHS) developed a draft protocol in 2013 for systematic evaluation of risk of bias in human and animal studies. A version of this draft protocol (which continues to evolve) has been adopted for use in this assessment of inorganic arsenic because it provides a unified approach for evaluating risk of bias from animal and epidemiology studies. The OHAT draft protocol includes 14 risk of bias questions grouped in five domains based on the type of potential bias: selection, performance, attrition, detection, and reporting bias. These questions, as discussed in Table 1-6 of the ADP, were derived by OHAT based on guidance from the Agency for Healthcare Research and Quality (AHRQ). The questions are intended to be applied on an outcome-specific basis when evaluating risk of bias (i.e., the rating for some questions depending on what types of health effects are of interest). Not all questions are applicable to both animal and epidemiology studies or to all types of study designs.

For each of these 15 questions, a reviewer assigns one of four standard risk of bias ratings, ranging from *definitely low* risk of bias to *definitely high* risk of bias (see Table 1-7). The rating assigned for each question is intended to represent the bias (or lack thereof) in the related methods and practices employed by the study authors. The set of ratings obtained for a study then can be used to inform an overall risk of bias conclusion for a study. Some of the questions can be assigned different ratings within a given study for different health outcomes, and therefore it is possible to obtain a range of outcome-specific ratings for a single study. Included in the draft OHAT protocol are guidelines for assigning ratings for each question, with separate guidance developed for review of epidemiology and animal studies. The draft OHAT risk of bias rating guidelines are included in Section 2.8 of this summary.

2.6.2 Assessing Risk of Bias for Arsenic Studies

For the evaluation of studies identified as potentially relevant to the hazard identification for inorganic arsenic, the draft OHAT risk of bias protocol was applied using the DRAGON database as a framework for managing and recording evaluation results and decisions. The goal of this aspect of the assessment was to assign a rating for each category for every study assessed as objectively as possible. Analysis of risk of bias,

however, necessarily requires subjective conclusions by an expert scientist. To increase consistency across the evaluations conducted in this assessment, each study was independently evaluated by two scientists, and each reviewer's assessment results were recorded independently in DRAGON. Assessment results included both the overall rating associated with a risk of bias question (i.e., ++, +, -, or --) and a written rationale supporting the rating. Reviewers referred to the draft OHAT protocol during their review (with key questions embedded in the DRAGON software for reference). In some cases, the draft OHAT guidelines were augmented with inorganic arsenic-specific guidelines developed for the current assessment. Any additions to the OHAT guidelines are also included in the tables in Attachment A and are clearly marked as specific to this assessment.

After independently reviewing a given inorganic arsenic study, the two assigned reviewers discussed and resolved any differences in ratings entered for a question. In some cases, tertiary review by a third senior scientist was conducted of individual ratings or the overall study (plus endpoint) conclusions, and additional quality control reviews were conducted for studies for which conclusions were not straightforward. The resolved ratings for each study were then considered to develop an overall risk of bias conclusion for the study. Because the ratings for some risk of bias questions can vary by health endpoint (e.g., some outcome assessment methods are more reliable than others), a range of overall risk of bias evaluations is possible for a given study (if multiple endpoints were considered in the study). The development of overall risk of bias evaluations for inorganic arsenic animal studies is discussed in Section 6.

The risk of bias evaluation process is time-intensive, requiring two scientists to review the full-text version of an article, develop responses to each question, resolve differences, and enter answers and conclusions for each question. Consequently, for the assessment of arsenic literature, an additional sorting step was conducted following the characterization step (described in Section 4) and before full risk of bias evaluation to identify studies ***less*** likely to be useful in the overall hazard identification for inorganic arsenic. This step uses several criteria to identify studies considered lower priority for hazard identification, and these studies were set aside without conducting a complete risk of bias evaluation. In addition, key data were not extracted from these studies into evidence tables. It is noted that these studies were not fully "excluded" from consideration for hazard identification; some studies might be used later in this assessment where additional evidence regarding health hazard is needed. Criteria used to identify these lower-priority epidemiology and animal studies are described in the following sections.

2.6.2.1 Prioritization and Assessing Risk of Bias in Epidemiology Studies

For epidemiology studies, all studies ***with*** a case-control, cohort, or cross-sectional design were subjected to a full risk of bias evaluation and were extracted into evidence tables. Other studies, including those designed as ecological studies, case series, and case reports, were not evaluated because individual-level exposure information is not used in the analyses and thus they provide less direct support for causal determinations. These studies might be used to provide further support in making causal inferences when other types of studies are not available. For example, some ecological studies are expected to provide supporting information regarding exposure during sensitive development times (e.g., in utero or childhood exposures) or exposure to susceptible populations.

Following this prioritization step, the risk of bias evaluation was conducted for all remaining epidemiology studies in accordance with the guidelines presented in the Appendix (Section 1.6 of the ADP). The results of the risk of bias evaluation are summarized in Section 4 and Section 5, which indicates ratings for each relevant risk of bias question.

2.6.2.2 Prioritization and Assessing Risk of Bias in Animal Arsenic Studies

For animal studies, studies that do not include adequate information relevant to hazard identification were eliminated from full risk of bias evaluation. Studies primarily focused on mode of action-related outcomes were not evaluated, including:

- mode of action studies presenting only data on liver weight for hazard identification; and
- mode of action studies presenting histopathology data with only descriptions and no incidence data reported.

Studies that only evaluated clinical chemistry endpoints as measures of liver toxicity were not evaluated, because this was considered to support clinical chemistry hazard identification rather than identification of liver effects. In addition, developmental studies that presented only pup weight, and/or studies without controls were not evaluated.

Following this prioritization step, the risk of bias evaluation was conducted for all remaining animal studies in accordance with the guidelines presented in Section 6.

2.7 Development of Evidence Tables for Hazard Identification

2.7.1 Epidemiology Data

2.7.1.1 Criteria for Identifying Primary Evidence Based on Risk of Bias

The results of the potential risk of bias evaluation were used to select studies for inclusion in evidence tables. Studies with the lowest potential risk of bias were selected to serve as the ***primary*** evidence supporting a causal relationship between inorganic arsenic exposure and outcomes for a given health effect category. Other relevant and useful studies, including those that may pose a higher risk of bias, were identified as providing ***supporting*** evidence. The most critical qualities of an epidemiology study with respect to risk of bias were identified to be:

- Confidence in the observed association based on a study design that allows for evaluation of an association between the exposure and the outcome;
- Confidence in the exposure assessment;
- Confidence in the outcome assessment; and
- Confidence in the overall internal validity of the study.

Of the risk of bias questions evaluated for epidemiology studies, six were selected as most informative for addressing these four critical study qualities.

- Question 3: Were the comparison groups appropriate? (*Confidence in observed association*)
- Question 4: Did the study design or analysis account for important confounding and modifying variables? (*Confidence in observed association*)
- Question 5: Did researchers adjust or control for other exposures that are anticipated to bias results? (*Confidence in observed association*)
- Question 12: Can we be confident in the exposure characterization? (*Confidence in exposure assessment*)
- Question 13: Can we be confident in the outcome assessment? (*Confidence in outcome assessment*)
- Question 15: Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)? (*Internal validity*)

Studies receiving a rating of *definitely* or *probably low risk of bias* (i.e., + or ++) for all six core questions were identified as primary evidence.

Studies receiving a rating of *definitely high risk of bias* (i.e., - -) for any of the six questions listed above were classified as supporting evidence. These studies might be

considered later in making causal determinations for an effect after evaluation of all primary evidence, but the information in these studies was not extracted into the current evidence tables.

Other studies classified as supporting include those receiving a rating of *probably high risk of bias* (–) for the following questions and combinations of questions:

- for all 3 observed association questions and exposure assessment and outcome assessment
- for 2 of the 3 observed association questions and *internal validity*
- for exposure assessment, outcome assessment, and internal validity
- for exposure assessment and 3 of the 4 questions for observed association and internal validity
- for exposure assessment and 2 of the 5 other questions for observed association, outcome assessment, and internal validity
- or *exposure assessment* and *unintended exposure* if the study is occupational
- for *exposure assessment* because the study did not measure arsenic (e.g., skin lesions versus no skin lesions or just control versus exposed with no arsenic measurements)

For the epidemiology studies meeting the criteria for "primary" studies, we reviewed the results of the evaluation of potential risk of bias and identified a subset of studies to include in the evidence tables. The evidence tables are not intended to be comprehensive, but rather to provide an overview of the more robust evidence. Thus, following the review of all primary studies, some were not included in the evidence tables. Any studies in this category of "primary but not included in evidence tables" are flagged with a footnote in the attached risk of bias summary tables. Primary studies not included in the evidence tables include studies focused on susceptibility factors, studies stratifying the population based on an existing disease, studies with inorganic arsenic water concentrations exceeding 150 µg/L, and some additional studies. These studies ***will*** be considered in the causal determination along with ecological studies, toxicology studies, and those with potentially high risk of bias (i.e., studies providing "supporting" evidence). In summary, studies selected for inclusion in the evidence tables are an overview of the available data supporting hazard identification.

2.7.1.2 **Creation of Evidence Tables**

Using the studies selected for inclusion in the evidence tables, data were extracted to support a weight of evidence discussion for on the basis of health outcome category. While the hazard identification tables provide an overview of all the information available for any given health effect system, the evidence tables provide more specific

information and present the specific data that support the strongest causal inference conclusions (e.g., using the Hill Criteria) regardless of results (positive, negative, or null).

In selecting specific study results and data to present in the evidence table, adjusted statistical estimates were presented rather than crude estimates when possible. All presented matrices of inorganic arsenic exposure (including water, hair, nails, urine) were selected when more than one was available. When multiple inorganic arsenic metrics were presented for the same exposure matrix, cumulative arsenic levels were selected preferentially over other metrics, when available. Total urinary arsenic levels were selected over concentrations of individual metabolites, when available. Within a health effect system, the different measures of the health effect (e.g., pinprick score in left leg, in right leg, in left arm, and in right arm) are included as separate columns in the table. All statistically significant results were included, regardless of health outcome. The null results were included for the main health effects, including lung cancer, bladder cancer, skin cancer, skin lesions, diabetes, and ischemic heart disease. Null results for the health effects not included in this list are described qualitatively.

2.7.2 Animal Data

2.7.2.1 Criteria for Identifying Primary Evidence Based on Risk of Bias

As with the epidemiology studies, toxicology studies with the lowest potential risk of bias were selected to serve as the primary evidence to demonstrate evidence of a causal relationship between inorganic arsenic exposure and outcomes for a given health effect category. For toxicology studies, confidence in the outcome assessment was considered to be the most critical quality of a study with respect to risk of bias (i.e., Question 13, "Can we be confident in the outcome assessment?"). Question 12 pertaining to exposure characterization (i.e., "Can we be confident in the exposure characterization?") was also considered to be of importance. Based on these assumptions, the following decision criteria were used to determine a study's utility with respect to evidence.

- Studies receiving ratings of either *definitely* or *probably low risk of bias* (i.e., + or ++) for Question 13 ***and also*** receiving the same ratings (i.e., + or ++) for at least half of the remaining questions were included as primary evidence for a given health effect.
- Studies receiving ratings of either *definitely* or *probably high risk of bias* (i.e., – or - -) for Question 13 ***and also*** receiving ratings of either *definitely* or *probably high risk of bias* (i.e., – or - -) for at least half of the remaining questions were judged to pose a high potential risk of bias. These studies were set aside to be reviewed after all other literature.

- Any studies receiving a rating of *definitely high risk of bias* (i.e., - -) for Question 12 were set aside for additional review.
- Studies that did not meet any of the above criteria were identified to be included as supporting evidence for a given health effect.

All animal studies identified as primary evidence for hazard identification based on the risk of bias evaluation were included in the evidence tables for inorganic arsenic.

2.7.2.2 Creation of Evidence Tables

The accompanying evidence tables present an overview of the available data for selected health effect categories, using the studies identified as primary evidence in the analysis of risk of bias. The tables are meant to summarize what is known about the effects of inorganic arsenic exposure in animals and do not include every outcome listed in every study. The following types of data were systematically omitted from data extraction and are not included in the attached evidence tables.

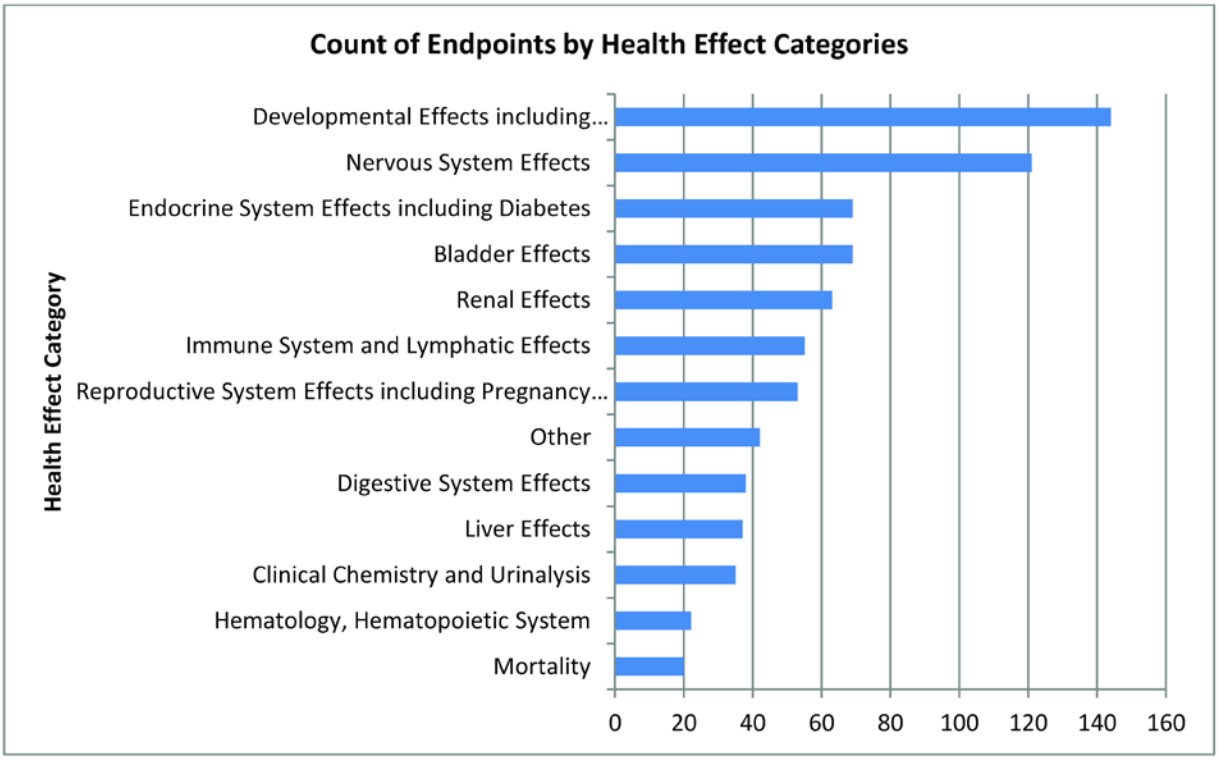
- Hematology, clinical chemistry, and urinalysis results.
- Histopathology results except when results are expected to potentially inform the causal determination for a health effect for which there is little epidemiologic data; in these cases, relevant significant and nonsignificant results were extracted.
- Organ weights, except data on thymus weights which immunologists consider a predictor of immune toxicity.
- Data on cytokines as this information more specifically informs mode of action determinations.
- Data presented in figures only; a qualitative description of the data was extracted.

2.8 Draft OHAT Guidance for Risk of Bias Evaluation and Assessment-specific Clarifications

Risk of bias questions and rating guidelines for epidemiology studies and animal studies are described in the ADP (Tables 1-10 and 1-11).

3 SUMMARY OF LITERATURE IDENTIFIED TO SUPPORT HAZARD IDENTIFICATION FOR INORGANIC ARSENIC

3.1 Overview of Epidemiology Studies Identified



3.1.1 Summary of Epidemiology Studies for Hazard Identification for Bladder Effects

Health Effect Category Route of Exposure Study Type	Count
Bladder Effects	**71**
Oral	63
Case-control	19
Cross-sectional	1
Cohort	14
Ecological	27
Other	2
Inhalation	7
Case-control	2
Cohort	3
Ecological	1
Other	1
Route Unknown	1
Case-control	1

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Bates et al. (1995)	Oral	United States	urinary bladder: neoplastic lesions
Bates et al. (2004)	Oral	Argentina	urinary bladder: neoplastic lesions
Chen et al. (1986)	Oral	Taiwan	urinary bladder: neoplastic lesions
Chen et al. (2003b)	Oral	Taiwan	urinary bladder: neoplastic lesions
Chung et al. (2011)	Oral	Taiwan	urinary bladder: neoplastic lesions
Chung et al. (2013)	Oral	Taiwan	urinary tract: neoplastic lesions
Feki-Tounsi et al. (2013)	Inhalation	Tunisia	urinary bladder: neoplastic lesions
Ferreccio et al. (2013b)	Oral	Chile	urinary bladder: neoplastic lesions
Hsu et al. (2008)	Oral	Taiwan	urinary tract: neoplastic lesions
Huang et al. (2008b)	Oral	Taiwan	urinary tract: neoplastic lesions
Karagas et al. (2004)	Oral	United States	urinary bladder: neoplastic lesions
Kurttio et al. (1999)	Oral	Finland	urinary bladder: neoplastic lesions
Meliker et al. (2010)	Oral	United States	urinary bladder: neoplastic lesions
Pu et al. (2007)	Oral	Taiwan	urinary bladder: neoplastic lesions
Steinmaus et al. (2003)	Oral	United States	urinary bladder: neoplastic lesions

Steinmaus et al. (2013)	Oral	Chile	urinary bladder: neoplastic lesions
Wang et al. (2009d)	Oral	Taiwan	urinary bladder: neoplastic lesions
Wu et al. (2012a)	Oral	Taiwan	urinary bladder: neoplastic lesions
Wu et al. (2013)	Oral	Taiwan, Province Of China	urinary tract: neoplastic lesions
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Michaud et al. (2004)	Inhalation	Finland	urinary bladder: neoplastic lesions
Michaud et al. (2004)	Oral	Finland	urinary bladder: neoplastic lesions
Michaud et al. (2004)	Route unknown	Finland	urinary bladder: neoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Baastrup et al. (2008)	Oral	Denmark	urinary bladder: neoplastic lesions
Chen et al. (2010b)	Oral	Taiwan	urinary tract: neoplastic lesions (2 Types)
Chiou et al. (1995)	Oral	Taiwan	urinary bladder: neoplastic lesions
Chiou et al. (2001a)	Oral	Taiwan	urinary tract: neoplastic lesions (2 Types)
Chung et al. (2012)	Oral	Taiwan	urinary bladder: neoplastic lesions
Cuzick et al. (1992)	Oral	United Kingdom	urinary bladder: neoplastic lesions
Hsu et al. (2013a)	Oral	Taiwan	urinary tract: neoplastic lesions
Huang et al. (2008a)	Oral	Taiwan	urinary tract: neoplastic lesions
Sawada et al. (2013)	Oral	Japan	urinary bladder: neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Enterline and Marsh (1982)	Inhalation	United States	urinary bladder: neoplastic lesions
Lewis et al. (1999)	Oral	United States	urinary tract: neoplastic lesions (2 Types)
Lubin et al. (1981)	Inhalation	United States	urinary bladder: neoplastic lesions
Pinto et al. (1978)	Inhalation	United States	urinary tract: neoplastic lesions
Tsuda et al. (1995)	Oral	Japan	urinary bladder: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Paul et al. (2013)	Oral	India	urine: parameters
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**

Buchet and Lison (1998)	Oral	Belgium	urinary bladder: neoplastic lesions
Chen et al. (1985)	Oral	Taiwan	urinary bladder: neoplastic lesions
Chen and Wang (1990)	Oral	Taiwan	urinary bladder: neoplastic lesions
Chen et al. (1992)	Oral	Taiwan	urinary bladder: neoplastic lesions
Fernández et al. (2012)	Oral	Chile	urinary bladder: neoplastic lesions
Guo et al. (1997)	Oral	Taiwan	urethra: neoplastic lesions
Guo et al. (1997)	Oral	Taiwan	urinary bladder: neoplastic lesions
Guo (2011)	Oral	Taiwan	urinary bladder: neoplastic lesions
Han et al. (2009)	Oral	United States	urinary bladder: neoplastic lesions
Hinwood et al. (1999)	Oral	Australia	urinary bladder: neoplastic lesions
Hopenhayn-Rich et al. (1996)	Oral	Argentina	urinary bladder: neoplastic lesions
Hopenhayn-Rich et al. (1998)	Oral	Argentina	urinary bladder: neoplastic lesions
Lamm et al. (2003)	Oral	Taiwan	urinary bladder: neoplastic lesions
Lamm et al. (2004)	Oral	United States	urinary bladder: neoplastic lesions
Marshall et al. (2007)	Oral	Chile	urinary bladder: neoplastic lesions
Meliker et al. (2007)	Oral	United States	urinary bladder: neoplastic lesions
Morales et al. (2000)	Oral	Taiwan	urinary bladder: neoplastic lesions
Mouly et al. (2012)	Oral	France	urinary bladder: neoplastic lesions
Pou et al. (2011)	Oral	Argentina	urinary bladder: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	urinary bladder: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	urinary bladder: neoplastic lesions
Smith et al. (1998)	Oral	Chile	urinary bladder: neoplastic lesions
Smith et al. (2012)	Oral	Chile	urinary bladder: neoplastic lesions
Su et al. (2011)	Oral	Taiwan	urinary bladder: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	urinary bladder: neoplastic lesions
Wu et al. (1989)	Oral	Taiwan	urinary bladder: neoplastic lesions
Yang et al. (2005)	Oral	Taiwan	urinary bladder: neoplastic lesions
Yorifuji et al. (2011)	Oral	Japan	urinary tract: neoplastic lesions
OTHER			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Begum et al. (2012)	Oral	United States, Taiwan, Bangladesh, West Bengal, Inner Mongolia, and China	urinary bladder: neoplastic lesions
Chu and Crawford-Brown (2006)	Oral	Various	urinary bladder: neoplastic lesions
Pinto et al. (1977)	Inhalation	United States	urinary bladder: neoplastic lesions

3.1.2 Summary of Epidemiology Studies for Hazard Identification for Cardiovascular Disease

Health Effect Category Route of Exposure Study Type	Count
Cardiovascular Disease	**181**
Oral	161
Case-control	14
Cross-sectional	74
Cohort	45
Ecological	23
Other	2
Inhalation	17
Case-control	4
Cross-sectional	1
Cohort	10
Other	2
Route Unknown	3
Cross-sectional	3

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE SERIES			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Mazumder (2003)	Oral	India	vascular: disease
Zaldívar (1980)	Oral	Chile	heart: function - ischemia
CASE-COHORT			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (2013b)	Oral	Bangladesh	cardiovascular disease (2 Types)
Chen et al. (2013b)	Oral	Bangladesh	cerebrovascular disease
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Axelson et al. (1978)	Inhalation	Sweden	vascular: disease
Chen et al. (1988)	Oral	Taiwan	vascular: disease
Ghosh (2013)	Oral	India	heart: function - unspecified
Ghosh (2013)	Oral	India	heart: neoplastic lesions
Ghosh (2013)	Oral	India	heart: nonneoplastic lesions

Lagerkvist et al. (1988)	Inhalation	Sweden	blood pressure: unspecified (3 Types)
Wu et al. (2006)	Oral	Taiwan	vascular: disease
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Hsieh et al. (2008a)	Oral	Taiwan	vascular: function (2 Types)
Hsieh et al. (2008b)	Oral	Taiwan	vascular: disease
Hsueh et al. (1998)	Oral	Taiwan	heart: function - ischemia
Kim et al. (2013)	Oral	United States	blood pressure: unspecified
Liao et al. (2009)	Oral	Taiwan	heart: function - rhythm (2 Types)
Wang et al. (2007c)	Oral	Taiwan	vascular: disease
Wu et al. (2010)	Oral	Taiwan	vascular: disease
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (1996)	Oral	Taiwan	heart: function - ischemia
Chen et al. (2006b)	Oral	Bangladesh	vascular: function
Chen et al. (2011b)	Oral	Bangladesh	vascular: disease (4 Types)
Chen et al. (2013c)	Oral	Bangladesh	heart: function - rhythm (3 Types)
Cuzick et al. (1992)	Oral	United Kingdom	vascular: disease
Gong and O'Bryant (2012)	Oral	United States	blood pressure: unspecified
Hawkesworth et al. (2013)	Oral	Bangladesh	blood pressure: unspecified (2 Types)
Liao et al. (2012)	Oral	Taiwan	cardiovascular disease (2 Types)
Moon et al. (2013)	Oral	United States	cardiovascular disease (4 Types)
Moon et al. (2013)	Oral	United States	cerebrovascular disease (2 Types)
Pi et al. (2005)	Oral	China	vascular: disease
Sohel et al. (2009)	Oral	Bangladesh	vascular: disease
Wang et al. (2002)	Oral	Taiwan	vascular: disease (3 Types)
Wang et al. (2010)	Oral	Taiwan	vascular: disease (2 Types)
Wang et al. (2011a)	Oral	Taiwan	blood pressure: unspecified
Wang et al. (2011a)	Oral	Taiwan	vascular: disease
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chiou et al. (2005)	Oral	Taiwan	vascular: disease
Enterline and Marsh (1982)	Inhalation	United States	cerebrovascular disease
Enterline and Marsh (1982)	Inhalation	United States	heart: function - contractility
Enterline and Marsh (1982)	Inhalation	United States	heart: nonneoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	vascular: disease
Hertz-Picciotto et al. (2000)	Oral	United States	cardiovascular system: nonneoplastic lesions

Jarup et al. (1989)	Inhalation	Sweden	heart: function - ischemia
Jarup et al. (1989)	Inhalation	Sweden	vascular: disease
Lewis et al. (1999)	Oral	United States	cardiovascular disease (7 Types)
Lewis et al. (1999)	Oral	United States	cerebrovascular disease
Lewis et al. (1999)	Oral	United States	vascular: disease
Lewis et al. (1999)	Oral	United States	vascular: function
Lubin et al. (1981)	Inhalation	United States	vascular: disease
Marsh et al. (2009)	Inhalation	United States	vascular: disease
Pinto et al. (1978)	Inhalation	United States	vascular: disease
Rahman et al. (1999a)	Oral	Bangladesh	blood pressure: unspecified
Wade et al. (2009)	Oral	China	heart: function - rhythm
Wade et al. (2009)	Oral	China	vascular: disease
Welch et al. (1982)	Inhalation	United States	heart: function - ischemia
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ahmad et al. (2006)	Oral	Bangladesh	heart: function - rhythm
Bosnjak et al. (2008)	Oral	Croatia	cardiovascular disease
Burgess et al. (2013)	Oral	United States, Mexico	vascular: disease
Chen et al. (2013a)	Oral	Bangladesh	cardiovascular disease
Chen et al. (1995)	Oral	Taiwan	blood pressure: unspecified
Chen et al. (2007b)	Oral	Bangladesh	blood pressure: diastolic
Chen et al. (2007b)	Oral	Bangladesh	blood pressure: systolic
Chen et al. (2007b)	Oral	Bangladesh	blood pressure: unspecified (2 Types)
Chen et al. (2012b)	Route unknown	Taiwan, Province Of China	blood pressure: unspecified (2 Types)
Chen et al. (2012b)	Route unknown	Taiwan, Province Of China	gene expression
Chiou et al. (1997)	Oral	Taiwan	vascular: disease (2 Types)
Chiou et al. (2001b)	Oral	Taiwan	vascular: disease
Guha Mazumder et al. (2012)	Oral	India	blood pressure: unspecified
Guo et al. (2007)	Oral	Mongolia	blood pressure: unspecified
Huang et al. (2007)	Oral	Taiwan	blood pressure: unspecified
Huang et al. (2009b)	Oral	Taiwan	vascular: disease
Islam et al. (2012a)	Oral	Bangladesh	blood pressure: diastolic
Islam et al. (2012a)	Oral	Bangladesh	blood pressure: systolic
Islam et al. (2012a)	Oral	Bangladesh	blood pressure: unspecified (3 Types)
Jensen and Hansen (1998)	Inhalation	Denmark	blood pressure: systolic
Jones et al. (2011)	Oral	United States	blood pressure: unspecified

Karim et al. (2013)	Oral	Bangladesh	antibody (B cell) mediated immunity: general (2 Types)
Karim et al. (2013)	Oral	Bangladesh	cholesterol (5 Types)
Karim et al. (2013)	Oral	Bangladesh	high sensitivity C reactive protein (hs-CRP)
Karim et al. (2013)	Oral	Bangladesh	inflammatory markers
Kim and Lee (2011)	Oral	South Korea	blood pressure: unspecified
Kunrath et al. (2013)	Oral	Romania	blood pressure: unspecified (12 Types)
Kwok et al. (2007)	Oral	China	blood pressure: diastolic
Kwok et al. (2007)	Oral	China	blood pressure: systolic
Li et al. (2013a)	Oral	China	blood pressure: unspecified
Li et al. (2009)	Oral	Taiwan	vascular: disease
Li et al. (2013b)	Oral	China	blood pressure: unspecified
Mordukhovich et al. (2009)	Oral	United States	heart: function - rhythm (2 Types)
Mumford et al. (2007)	Oral	China	heart: function - rhythm (2 Types)
Osorio-Yáñez et al. (2013)	Oral	Mexico	cardiovascular disease (2 Types)
Rahman and Axelson (2001)	Oral	Bangladesh	blood pressure: unspecified
Tseng et al. (1996)	Oral	Taiwan	vascular: disease
Tseng et al. (1997)	Oral	Taiwan	vascular: disease
Tseng et al. (2003)	Oral	Taiwan	heart: function - ischemia
Wang et al. (2009a)	Oral	Taiwan	heart: function - rhythm (11 Types)
Xia et al. (2009)	Oral	China	cardiovascular disease
Xia et al. (2009)	Oral	China	cerebrovascular disease
Yildiz et al. (2008)	Oral	Turkey	heart: function - contractility
Zhang et al. (2013a)	Oral	China	blood pressure: unspecified
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Buchet and Lison (1998)	Oral	Belgium	heart: nonneoplastic lesions
Chang et al. (2004)	Oral	Taiwan	heart: function - ischemia
Cheng et al. (2010)	Oral	Taiwan	vascular: disease
Chiu et al. (2007)	Oral	Taiwan	vascular: disease
Dastgiri et al. (2010)	Oral	Iran	blood pressure: unspecified
Engel and Smith (1994)	Oral	United States	vascular: disease
Jovanović et al. (2012)	Oral	Serbia	vascular: function
Lisabeth et al. (2010)	Oral	United States	vascular: disease
Medrano et al. (2010)	Oral	Spain	vascular: disease
Meliker et al. (2007)	Oral	United States	vascular: disease
Tsai et al. (1999)	Oral	Taiwan	blood pressure: unspecified
Tsai et al. (1999)	Oral	Taiwan	heart: function - ischemia
Tsai et al. (1999)	Oral	Taiwan	vascular: disease
Tseng (1977)	Oral	Taiwan	vascular: disease
Tseng (1989)	Oral	Taiwan	vascular: disease

Tseng et al. (2005)	Oral	Taiwan	vascular: disease
Valentine et al. (1992)	Oral	United States	clinical observation
Varsányi et al. (1991)	Oral	Hungary	vascular: disease
Wang et al. (2003)	Oral	Taiwan	vascular: disease
Wu et al. (1989)	Oral	Taiwan	vascular: disease
Yang (2006)	Oral	Taiwan	vascular: disease
Yeh (1973)	Oral	Taiwan	vascular: disease
Yuan et al. (2007)	Oral	Chile	vascular: disease
OTHER			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Lagerkvist et al. (1986)	Inhalation	Sweden	vascular: function
Pinto et al. (1977)	Inhalation	United States	heart: function - ischemia

3.1.3 Summary of Epidemiology Studies for Hazard Identification for Clinical Chemistry and Urinalysis

Health Effect Category Route of Exposure Study Type	Count
Clinical Chemistry and Urinalysis	**35**
Oral	27
Case-control	5
Cross-sectional	21
Cohort	1
Inhalation	3
Cross-sectional	3
Route Unknown	5
Case-control	5

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Nabi et al. (2005)	Oral	Bangladesh	alanine aminotransferase (ALT)
Nabi et al. (2005)	Oral	Bangladesh	alkaline phosphatase (ALP)
Nabi et al. (2005)	Oral	Bangladesh	aspartate aminotransferase (AST)
Nabi et al. (2005)	Oral	Bangladesh	cholesterol
Shen et al. (2013)	Route unknown	China	urine: parameters (5 Types)
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Kim et al. (2013)	Oral	United States	albumin
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (2011c)	Oral	Bangladesh	total protein
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Casale et al. (2013)	Inhalation	Italy	alanine aminotransferase (ALT)
Casale et al. (2013)	Oral	Italy	alanine aminotransferase (ALT)
Casale et al. (2013)	Inhalation	Italy	aspartate aminotransferase (AST)

Casale et al. (2013)	Oral	Italy	aspartate aminotransferase (AST)
Casale et al. (2013)	Inhalation	Italy	gamma-glutamyl transpeptidase (GGT)
Casale et al. (2013)	Oral	Italy	gamma-glutamyl transpeptidase (GGT)
Das et al. (2012a)	Oral	India	alanine aminotransferase (ALT)
Das et al. (2012a)	Oral	India	alkaline phosphatase (ALP)
Das et al. (2012a)	Oral	India	aspartate aminotransferase (AST)
Das et al. (2012a)	Oral	India	bilirubin
Islam et al. (2011)	Oral	Bangladesh	alanine aminotransferase (ALT)
Islam et al. (2011)	Oral	Bangladesh	alkaline phosphatase (ALP)
Islam et al. (2011)	Oral	Bangladesh	aspartate aminotransferase (AST)
Maiti et al. (2012)	Oral	India	alanine aminotransferase (ALT)
Maiti et al. (2012)	Oral	India	albumin
Maiti et al. (2012)	Oral	India	alkaline phosphatase (ALP)
Maiti et al. (2012)	Oral	India	aspartate aminotransferase (AST)
Maiti et al. (2012)	Oral	India	bilirubin
Maiti et al. (2012)	Oral	India	creatinine
Maiti et al. (2012)	Oral	India	gamma-glutamyl transpeptidase (GGT)
Maiti et al. (2012)	Oral	India	globulin
Maiti et al. (2012)	Oral	India	total protein
Maiti et al. (2012)	Oral	India	uric acid
Mazumder et al. (2013)	Oral	India	urine: parameters

3.1.4 Summary of Epidemiology Studies for Hazard Identification for Developmental Effects including Neurodevelopmental

Health Effect Category Route of Exposure Study Type	Count
Developmental Effects including Neurod	**166**
Oral	123
Case-control	2
Cross-sectional	76
Cohort	36
Ecological	8
Other	1
Inhalation	16
Case-control	1
Cross-sectional	7
Cohort	6
Ecological	2
In Utero	10
Cohort	10
Route Unknown	17
Cross-sectional	11
Cohort	6

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

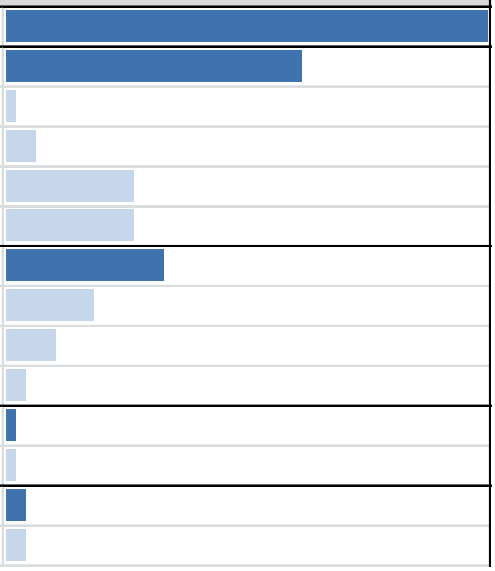
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Jin et al. (2013)	Inhalation	China	congenital malformation
Jin et al. (2013)	Oral	China	congenital malformation
Zierler et al. (1988)	Oral	United States	congenital malformation
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Gardner et al. (2013)	Inhalation	Bangladesh	developmental milestone (6 Types)
Gardner et al. (2013)	Oral	Bangladesh	developmental milestone (6 Types)
Gardner et al. (2013)	In utero	Bangladesh	developmental milestone (6 Types)
Gardner et al. (2013)	Route unknown	Bangladesh	developmental milestone (6 Types)
Hamadani et al. (2010)	Oral	Bangladesh	CNS: function - cognition (4 Types)

Hamadani et al. (2011)	Oral	Bangladesh	CNS: function - cognition (3 Types)
Hopenhayn et al. (2003)	Oral	Chile	birth weight
Huyck et al. (2007)	Oral	Bangladesh	birth weight
Rahman et al. (2007)	Oral	Bangladesh	neonatal/infant mortality (3 Types)
Rahman et al. (2007)	Oral	Bangladesh	number of dead fetuses
Rahman et al. (2009)	Oral	Bangladesh	birth length
Rahman et al. (2009)	Oral	Bangladesh	birth weight
Rahman et al. (2009)	Oral	Bangladesh	growth
Rahman et al. (2009)	Oral	Bangladesh	head circumference
Rahman et al. (2010)	Oral	Bangladesh	neonatal/infant mortality
Saha et al. (2012)	Oral	Bangladesh	growth (6 Types)
Tofail et al. (2009)	Oral	Bangladesh	CNS: function - behavioral
Tofail et al. (2009)	In utero	Bangladesh	CNS: function - behavioral
Tofail et al. (2009)	Oral	Bangladesh	CNS: function - cognition (2 Types)
Tofail et al. (2009)	In utero	Bangladesh	CNS: function - cognition (2 Types)
Tofail et al. (2009)	Oral	Bangladesh	motor activity
Tofail et al. (2009)	In utero	Bangladesh	motor activity
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Sen and Chaudhuri (2007)	Oral	India	age at first estrous/menses
Sohel et al. (2010)	Oral	Bangladesh	neonatal/infant mortality
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Calderon et al. (2001)	Inhalation	Mexico	CNS: function - cognition (7 Types)
Calderon et al. (2001)	Oral	Mexico	CNS: function - cognition (7 Types)
Chakraborti et al. (2003)	Oral	India	birth weight
Gelmann et al. (2013)	Oral	Romania	birth weight
Guan et al. (2012)	Oral	China	birth height birth heightt console birth height
Guan et al. (2012)	Oral	China	birth weight
Guan et al. (2012)	Oral	China	chest circumference
Guan et al. (2012)	Oral	China	head circumference
Khan et al. (2012)	Oral	Bangladesh	CNS: function - cognition (3 Types)
Kippler et al. (2012)	Oral	Bangladesh	growth (4 Types)
Kippler et al. (2012)	Oral	Bangladesh	head circumference
Kwok et al. (2006)	Oral	Bangladesh	birth weight (3 Types)
Kwok et al. (2006)	Oral	Bangladesh	external malformation
Milton et al. (2005)	Oral	Bangladesh	neonatal/infant mortality
Mukherjee et al. (2005)	Oral	India	birth weight
Mukherjee et al. (2005)	Oral	India	neonatal/infant mortality
Nahar et al. (2014)	Oral	Bangladesh	CNS: function - behavioral

Nahar et al. (2014)	Oral	Bangladesh	IQ
Parvez et al. (2011)	Oral	Bangladesh	CNS: function - cognition (5 Types)
Rocha-Amador et al. (2007)	Oral	Mexico	CNS: function - cognition (3 Types)
Roy et al. (2011)	Oral	Mexico	CNS: function - behavioral (4 Types)
Tsai et al. (2003)	Oral	Taiwan	CNS: function - behavioral (4 Types)
Vall et al. (2012)	Oral	Spain	birth length
Vall et al. (2012)	Oral	Spain	birth weight
Vall et al. (2012)	Oral	Spain	gestational age at birth (humans)
Vall et al. (2012)	Oral	Spain	head circumference
Vall et al. (2012)	Oral	Spain	preterm birth/delivery (<37 weeks)
Von Ehrenstein et al. (2006)	Oral	India	neonatal/infant mortality (2 Types)
von Ehrenstein et al. (2007)	Oral	India	CNS: function - cognition (10 Types)
Wang et al. (2007a)	Oral	Bangladesh	CNS: function - cognition
Wasserman et al. (2004)	Oral	Bangladesh	CNS: function - cognition (3 Types)
Wasserman et al. (2007)	Oral	Bangladesh	CNS: function - cognition (4 Types)
Wasserman et al. (2011)	Oral	Bangladesh	CNS: function - cognition (5 Types)
Wright et al. (2006)	Route unknown	United States	developmental milestone (8 Types)
Wright et al. (2006)	Route unknown	United States	IQ (3 Types)
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Aelion et al. (2013)	Inhalation	United States	birth weight
Chakraborti et al. (2013a)	Oral	Bangladesh; India	birth weight (2 Types)
Cherry et al. (2010)	Oral	Bangladesh	neonatal/infant mortality
Engel and Smith (1994)	Oral	United States	congenital malformation
Gerr et al. (2000)	Inhalation	United States	CNS: function - behavioral
Hopenhayn-Rich et al. (1999)	Oral	Chile	neonatal/infant mortality
Hopenhayn-Rich et al. (2000)	Oral	Chile	neonatal/infant mortality
Myers et al. (2010)	Oral	China	birth weight
Myers et al. (2010)	Oral	China	neonatal/infant mortality
OTHER			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Dong and Su (2009)	Oral	China	CNS: function - cognition

3.1.5 Summary of Epidemiology Studies for Hazard Identification for Digestive System Effects

Health Effect Category Route of Exposure Study Type	Count
Digestive System Effects	**49**
Oral	30
Case-control	1
Cross-sectional	3
Cohort	13
Ecological	13
Inhalation	16
Cohort	9
Ecological	5
Other	2
Dermal	1
Other	1
In Utero	2
Cohort	2



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

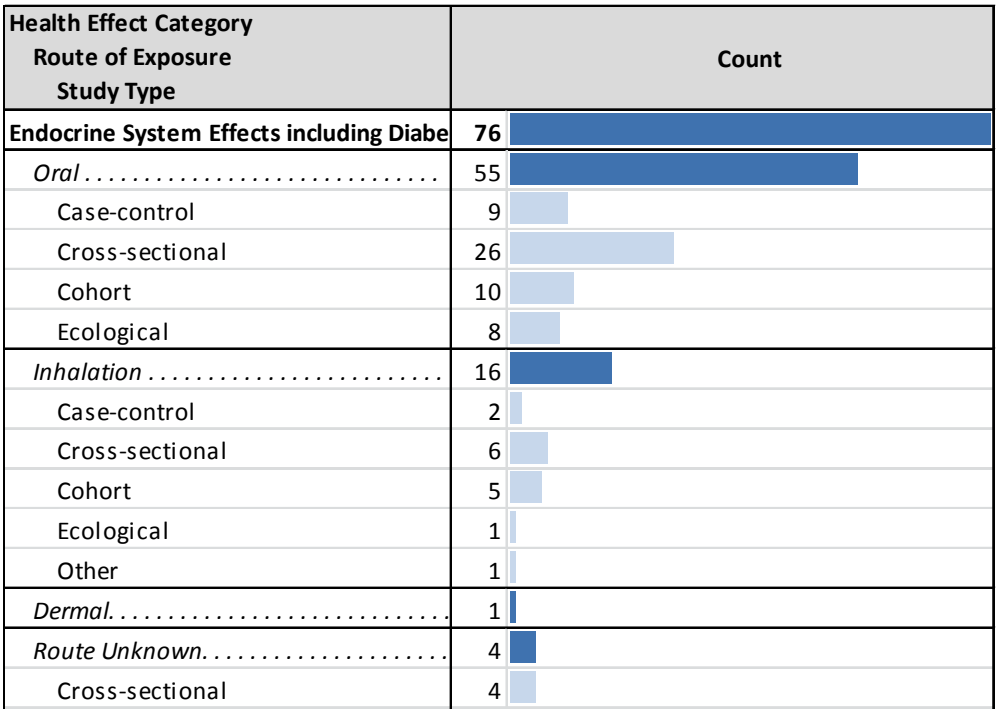
CASE REPORT			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Kerr (1875)	Inhalation	United Kingdom	clinical observation
Kerr (1875)	Dermal	United Kingdom	clinical observation
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Amaral et al. (2012)	Oral	Spain	pancreas: neoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Baastrup et al. (2008)	Oral	Denmark	digestive system: neoplastic lesions
Farzan et al. (2013)	In utero	United States	diarrhea
García-Esquinas et al. (2013)	Oral	United States	large intestine: neoplastic lesions
García-Esquinas et al. (2013)	Oral	United States	stomach: neoplastic lesions

Hsu et al. (2013b)	Oral	Taiwan	large intestine: neoplastic lesions (2 Types)
Hsu et al. (2013b)	Oral	Taiwan	stomach: neoplastic lesions
Rahman et al. (2011)	Oral	Bangladesh	diarrhea
Rahman et al. (2011)	In utero	Bangladesh	diarrhea
Sawada et al. (2013)	Oral	Japan	digestive system: neoplastic lesions
Sawada et al. (2013)	Oral	Japan	stomach: neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Bulbulyan et al. (1996)	Inhalation	Russia	stomach: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	digestive system: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	large intestine: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	stomach: nonneoplastic lesions
Kreuzer et al. (2012)	Inhalation	Germany	stomach: neoplastic lesions
Lewis et al. (1999)	Oral	United States	digestive system: neoplastic lesions
Lewis et al. (1999)	Oral	United States	large intestine: neoplastic lesions
Lewis et al. (1999)	Oral	United States	stomach: neoplastic lesions
Lubin et al. (1981)	Inhalation	United States	digestive system: neoplastic lesions (2 Types)
Lubin et al. (1981)	Inhalation	United States	digestive system: nonneoplastic lesions
Pinto et al. (1978)	Inhalation	United States	digestive system: neoplastic lesions
Tsuda et al. (1995)	Oral	Japan	large intestine: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Syed et al. (2013)	Oral	Bangladesh	oral cavity: nonneoplastic lesions (3 Types)
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Cebrián et al. (1983)	Oral	Mexico	clinical observation
Chen et al. (1985)	Oral	Taiwan	large intestine: neoplastic lesions
Hinwood et al. (1999)	Oral	Australia	digestive system: neoplastic lesions
Hopenhayn-Rich et al. (1996)	Oral	Argentina	stomach: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	digestive system: neoplastic lesions (3 Types)
Rivara et al. (1997)	Oral	Chile	digestive system: neoplastic lesions (3 Types)
Rivara et al. (1997)	Inhalation	Chile	esophagus: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	esophagus: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	stomach: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	stomach: neoplastic lesions

Tsai et al. (1999)	Oral	Taiwan	digestive system: neoplastic lesions
Valentine et al. (1992)	Oral	United States	clinical observation
Wu et al. (1989)	Oral	Taiwan	digestive system: neoplastic lesions
Yang et al. (2008b)	Oral	Taiwan	large intestine: neoplastic lesions
OTHER			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Pinto et al. (1977)	Inhalation	United States	digestive system: neoplastic lesions

3.1.6 Summary of Epidemiology Studies for Hazard Identification for Endocrine System Effects including Diabetes

Health Effect Category Route of Exposure Study Type	Count
Endocrine System Effects including Diabe	**76**
Oral	55
Case-control	9
Cross-sectional	26
Cohort	10
Ecological	8
Inhalation	16
Case-control	2
Cross-sectional	6
Cohort	5
Ecological	1
Other	1
Dermal	1
Route Unknown	4
Cross-sectional	4



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

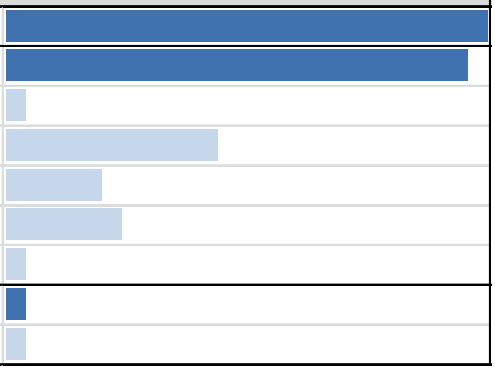
CASE-COHORT			
Study References	**Route of Exposure**	**Country**	**Health Effect**
James et al. (2013)	Oral	United States	diabetes mellitus
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Coronado-González et al. (2007)	Oral	Mexico	diabetes, type 2
Nizam et al. (2013)	Oral	Bangladesh	diabetes mellitus
Pan et al. (2013)	Oral	Bangladesh	diabetes, type 2
Rahman and Axelson (1995)	Inhalation	Sweden	diabetes mellitus
Rahman et al. (1996)	Inhalation	Sweden	diabetes mellitus
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Hsieh et al. (2008a)	Oral	Taiwan	growth hormone
Hsieh et al. (2008a)	Oral	Taiwan	testosterone (2 Types)

Kim et al. (2013)	Oral	United States	blood: glucose (2 Types)
Kim et al. (2013)	Oral	United States	diabetes mellitus
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (2012a)	Oral	Taiwan	diabetes mellitus
Ettinger et al. (2009)	Oral	United States	gestational diabetes
García-Esquinas et al. (2013)	Oral	United States	pancreas: neoplastic lesions
Hsu et al. (2013b)	Oral	Taiwan	diabetes mellitus
Hsu et al. (2013b)	Oral	Taiwan	pancreas: neoplastic lesions
Sawada et al. (2013)	Oral	Japan	pancreas: neoplastic lesions
Tseng et al. (2000)	Oral	Taiwan	diabetes mellitus
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Enterline and Marsh (1982)	Inhalation	United States	diabetes mellitus (2 Types)
Enterline and Marsh (1982)	Inhalation	United States	thyroid gland: neoplastic lesions
Lewis et al. (1999)	Oral	United States	diabetes mellitus
Lewis et al. (1999)	Oral	United States	pancreas: neoplastic lesions
Lubin et al. (1981)	Inhalation	United States	endocrine system: nonneoplastic lesions (2 Types)
Rahman et al. (1998)	Oral	Bangladesh	diabetes mellitus
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (2010c)	Oral	Bangladesh	diabetes mellitus
Chen et al. (2010c)	Oral	Bangladesh	urine: glucose
Chen et al. (2011a)	Oral	Taiwan	diabetes mellitus
Ciarrocca et al. (2012)	Inhalation	Italy	diabetes mellitus
Ciarrocca et al. (2012)	Inhalation	Italy	thyroglobulin
Ciarrocca et al. (2012)	Inhalation	Italy	thyroid stimulating hormone (TSH)
Ciarrocca et al. (2012)	Inhalation	Italy	thyroxine (T4)
Ciarrocca et al. (2012)	Inhalation	Italy	triiodothyronine (T3)
Del Razo et al. (2011)	Oral	Mexico	diabetes mellitus
Del Razo et al. (2011)	Oral	Mexico	insulin
Del Razo et al. (2011)	Oral	Mexico	insulin resistance
Drobná et al. (2013)	Oral	Mexico	diabetes mellitus
Gribble et al. (2012)	Oral	United States	diabetes mellitus
Guo et al. (2007)	Oral	Mongolia	urine: glucose
Islam et al. (2012b)	Oral	Bangladesh	diabetes, type 2
Jensen and Hansen (1998)	Inhalation	Denmark	blood: glucose
Jovanovic et al. (2013)	Oral	Serbia	diabetes, type 2
Kim and Lee (2011)	Oral	South Korea	diabetes mellitus
Lai et al. (1994)	Oral	Taiwan	diabetes mellitus

Li et al. (2013a)	Oral	China	diabetes, type 2
Maiti et al. (2012)	Oral	India	blood: glucose
Makris et al. (2012)	Oral	Cyprus	diabetes, type 2
Meeker et al. (2009)	Oral	United States	prolactin (PRL)
Meeker et al. (2009)	Oral	United States	thyroid stimulating hormone (TSH)
Navas-Acien et al. (2008)	Oral	United States	diabetes, type 2
Navas-Acien et al. (2009)	Oral	United States	diabetes, type 2
Rahman et al. (1999b)	Oral	Bangladesh	urine: glucose (2 Types)
Rahman and Axelson (2001)	Oral	Bangladesh	urine: glucose
Rhee et al. (2013)	Route unknown	Korea, Republic Of	diabetes mellitus
Rhee et al. (2013)	Route unknown	Korea, Republic Of	glucose stimulated insulin secretion
Rhee et al. (2013)	Route unknown	Korea, Republic Of	impaired glucose tolerance
Rhee et al. (2013)	Route unknown	Korea, Republic Of	insulin resistance
Steinmaus et al. (2009)	Oral	United States	diabetes, type 2
Zierold et al. (2004)	Oral	United States	diabetes, type 2
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chang et al. (1991)	Oral	Taiwan	thyroid gland: gross pathology
Chiu et al. (2006)	Oral	Taiwan	diabetes mellitus
Liu-Mares et al. (2013)	Oral	United States	pancreas: neoplastic lesions
Meliker et al. (2007)	Oral	United States	diabetes mellitus
Rivara et al. (1997)	Inhalation	Chile	pancreas: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	pancreas: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	diabetes mellitus
Wang et al. (2003)	Oral	Taiwan	diabetes mellitus
Yorifuji et al. (2011)	Oral	Japan	pancreas: neoplastic lesions
META-ANALYSIS			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Wang et al. (2014)	Inhalation		diabetes, type 2
Wang et al. (2014)	Oral		diabetes, type 2
Wang et al. (2014)	Dermal		diabetes, type 2
OTHER			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ojajarvi et al. (2000)	Inhalation	Multiple	pancreas: neoplastic lesions

3.1.7 Summary of Epidemiology Studies for Hazard Identification for Hematology, Hematopoietic System

Health Effect Category Route of Exposure Study Type	Count
Hematology, Hematopoietic System	**25**
Oral	24
Case-control	1
Cross-sectional	11
Cohort	5
Ecological	6
Other	1
Inhalation	1
Ecological	1



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE SERIES			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Mazumder (2003)	Oral	India	anemia
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ghosh (2013)	Oral	India	blood: coagulation/thrombosis
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Hopenhayn et al. (2006)	Oral	Chile	hematocrit (packed cell volume)
Saha et al. (2013)	Oral	Bangladesh	hematocrit (packed cell volume)
Saha et al. (2013)	Oral	Bangladesh	hemoglobin
Saha et al. (2013)	Oral	Bangladesh	leukocyte count
Saha et al. (2013)	Oral	Bangladesh	leukocyte differential
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Del Razo et al. (2011)	Oral	Mexico	HbA1c
Guo et al. (2007)	Oral	Mongolia	blood: oxygen
Heck et al. (2008)	Oral	Bangladesh	hemoglobin
Maiti et al. (2012)	Oral	India	erythrocyte count

Maiti et al. (2012)	Oral	India	hematocrit (packed cell volume)
Maiti et al. (2012)	Oral	India	hemoglobin
Maiti et al. (2012)	Oral	India	leukocyte count
Maiti et al. (2012)	Oral	India	leukocyte differential
Maiti et al. (2012)	Oral	India	mean corpuscular hemoglobin concentration
Maiti et al. (2012)	Oral	India	mean corpuscular volume
Majumdar et al. (2009)	Oral	India	hemoglobin
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Buchet and Lison (1998)	Oral	Belgium	bone marrow: nonneoplastic lesions
Buchet and Lison (1998)	Oral	Belgium	leukemia
Hinwood et al. (1999)	Oral	Australia	leukemia
Rivara et al. (1997)	Inhalation	Chile	leukemia
Rivara et al. (1997)	Oral	Chile	leukemia
Wu et al. (1989)	Oral	Taiwan	leukemia
Yorifuji et al. (2011)	Oral	Japan	hematopoietic system: neoplastic lesions

3.1.8 Summary of Epidemiology Studies for Hazard Identification for Liver Effects

Health Effect Category Route of Exposure Study Type	Count
Liver Effects	**39**
Oral	36
Case-control	3
Cross-sectional	4
Cohort	7
Ecological	18
Other	4
Inhalation	3
Cohort	2
Ecological	1

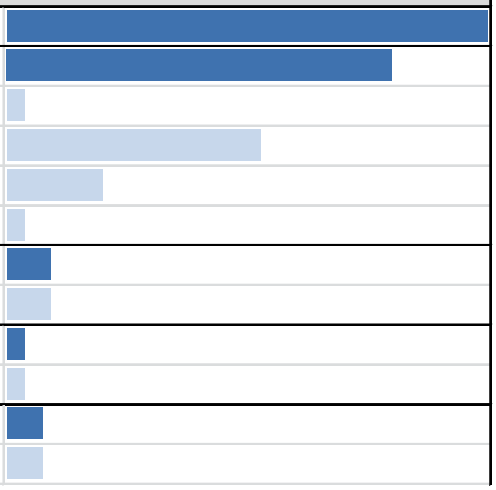
Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE REPORT			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Morris et al. (1974)	Oral	United Kingdom	liver: nonneoplastic lesions
Zaldívar et al. (1981)	Oral	Chile	liver: nonneoplastic lesions
CASE SERIES			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Datta et al. (1979)	Oral	India	liver: nonneoplastic lesions
Mazumder (2003)	Oral	India	clinical observation
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (1986)	Oral	Taiwan	liver: neoplastic lesions
Ghosh (2013)	Oral	India	liver: gross pathology
Wadhwa et al. (2011a)	Oral	Pakistan	liver: neoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Baastrup et al. (2008)	Oral	Denmark	liver: neoplastic lesions
Chung et al. (2012)	Oral	Taiwan	liver: neoplastic lesions

García-Esquinas et al. (2013)	Oral	United States	liver: neoplastic lesions
Hsu et al. (2013b)	Oral	Taiwan	liver: neoplastic lesions
Sawada et al. (2013)	Oral	Japan	liver: neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Enterline and Marsh (1982)	Inhalation	United States	liver: nonneoplastic lesions (2 Types)
Lewis et al. (1999)	Oral	United States	liver: neoplastic lesions
Tsuda et al. (1995)	Oral	Japan	liver: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Guo et al. (2007)	Oral	Mongolia	liver: nonneoplastic lesions (2 Types)
Majumdar et al. (2009)	Oral	India	liver: gross pathology
Paul et al. (2013)	Oral	India	liver: neoplastic lesions
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Buchet and Lison (1998)	Oral	Belgium	liver: nonneoplastic lesions
Chen et al. (1985)	Oral	Taiwan	liver: neoplastic lesions
Chen and Wang (1990)	Oral	Taiwan	liver: neoplastic lesions
Chen et al. (1992)	Oral	Taiwan	liver: neoplastic lesions
Guo (2003)	Oral	Taiwan	liver: neoplastic lesions
Han et al. (2009)	Oral	United States	liver: neoplastic lesions
Hinwood et al. (1999)	Oral	Australia	liver: neoplastic lesions
Hopenhayn-Rich et al. (1998)	Oral	Argentina	liver: neoplastic lesions
Liaw et al. (2008)	Oral	Chile	liver: neoplastic lesions
Lin et al. (2013)	Oral	Taiwan	liver: neoplastic lesions
Meliker et al. (2007)	Oral	United States	liver: neoplastic lesions
Morales et al. (2000)	Oral	Taiwan	liver: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	liver: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	liver: neoplastic lesions
Smith et al. (1998)	Oral	Chile	liver: neoplastic lesions
Smith et al. (2012)	Oral	Chile	liver: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	liver: nonneoplastic lesions
Wu et al. (1989)	Oral	Taiwan	liver: neoplastic lesions
Yorifuji et al. (2011)	Oral	Japan	liver: neoplastic lesions

3.1.9 Summary of Epidemiology Studies for Hazard Identification for Immune System and Lymphatic Effects

Health Effect Category Route of Exposure Study Type	Count
Immune System and Lymphatic Effects	**55**
Oral	44
Case-control	2
Cross-sectional	29
Cohort	11
Ecological	2
Inhalation	5
Cohort	5
In Utero	2
Cohort	2
Route Unknown	4
Cross-sectional	4



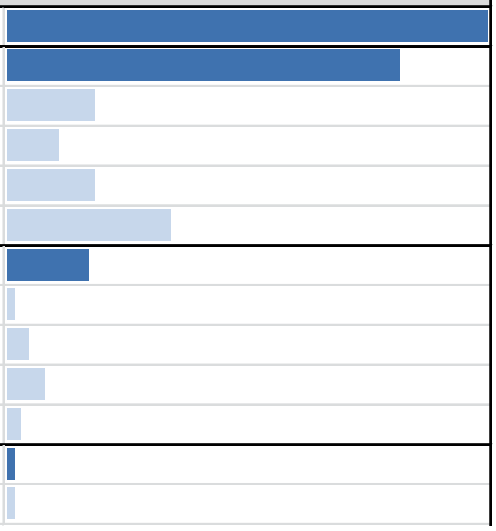
Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Infante-Rivard et al. (2001)	Oral	Canada	leukemia
Lu and Chen (1991)	Oral	Taiwan	cell-mediated immunity effects
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ahmed et al. (2012)	In utero	Bangladesh	thymus: function
Ahmed et al. (2012)	In utero	Bangladesh	thymus: gross pathology
García-Esquinas et al. (2013)	Oral	United States	lymph node: neoplastic lesions
Moore et al. (2009)	Oral	Bangladesh	thymus: absolute weight
Moore et al. (2009)	Oral	Bangladesh	thymus: relative weight
Raqib et al. (2009)	Oral	Bangladesh	nonspecific/innate immunity effects
Raqib et al. (2009)	Oral	Bangladesh	T cells
Raqib et al. (2009)	Oral	Bangladesh	thymus: function (3 Types)
Saha et al. (2013)	Oral	Bangladesh	immunoglobulin
Sohel et al. (2009)	Oral	Bangladesh	clinical observation
COHORT (RETROSPECTIVE)			
Study References	**Route of**	**Country**	**Health Effect**

	Exposure		
Enterline and Marsh (1982)	Inhalation	United States	lymphoma
Lewis et al. (1999)	Oral	United States	lymphoma
Lubin et al. (1981)	Inhalation	United States	lymphoma (2 Types)
Marsh et al. (2009)	Inhalation	United States	clinical observation
Pinto et al. (1978)	Inhalation	United States	lymphoma
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Biswas et al. (2008)	Oral	India	cell (T cell) mediated immunity: general
Biswas et al. (2008)	Oral	India	nonspecific/innate immunity effects (6 Types)
Bosnjak et al. (2008)	Oral	Croatia	nonspecific/innate immunity effects
Islam et al. (2007)	Oral	Bangladesh	immunoglobulin
Josyula et al. (2006)	Oral	United States	nonspecific/innate immunity effects (5 Types)
Mazumder et al. (2000)	Oral	India	clinical observation
Milton et al. (2001)	Oral	Bangladesh	clinical observation
Milton and Rahman (2002)	Oral	Bangladesh	clinical observation
Pesola et al. (2012)	Oral	Bangladesh	clinical observation
Shiue (2013)	Oral	United States	immediate-type hypersensitivity response (4 Types)
Shiue (2013)	Route unknown	United States	immediate-type hypersensitivity response (4 Types)
Von Ehrenstein et al. (2005)	Oral	India	clinical observation
Wu et al. (2012b)	Oral	Bangladesh	inflammatory markers (6 Types)
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Han et al. (2009)	Oral	United States	lymphoma
Tsai et al. (1999)	Oral	Taiwan	lymphoma

3.1.10 Summary of Epidemiology Studies for Hazard Identification for Renal Effects

Health Effect Category Route of Exposure Study Type	Count
Renal Effects	**65**
Oral	53
Case-control	12
Cross-sectional	7
Cohort	12
Ecological	22
Inhalation	11
Case-control	1
Cross-sectional	3
Cohort	5
Ecological	2
Route Unknown	1
Case-control	1



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

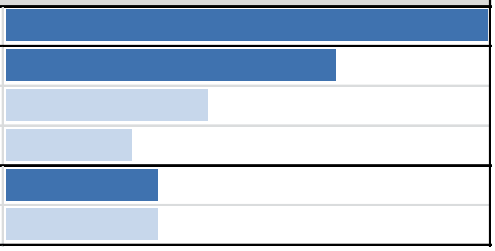
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Boffetta et al. (2011)	Inhalation	Czech Republic; Poland; Romania; Russian Federation	kidney: nonneoplastic lesions
Feng et al. (2013)	Oral	China	kidney: function
Feng et al. (2013)	Oral	China	urine: parameters
Ferreccio et al. (2013a)	Oral	Chile	kidney: neoplastic lesions (3 Types)
Ferreccio et al. (2013a)	Oral	Chile	ureter: neoplastic lesions
Huang et al. (2011)	Oral	Taiwan	kidney: neoplastic lesions
Huang et al. (2012)	Oral	Taiwan	kidney: neoplastic lesions
Kurttio et al. (1999)	Oral	Finland	kidney: neoplastic lesions
Mostafa and Cherry (2013)	Oral	Bangladesh	kidney: neoplastic lesions (3 Types)
Palaneeswari et al. (2013)	Route unknown	India	kidney: function

COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Baastrup et al. (2008)	Oral	Denmark	kidney: neoplastic lesions
Enterline et al. (1995)	Inhalation	United States	kidney: neoplastic lesions
García-Esquinas et al. (2013)	Oral	United States	kidney: neoplastic lesions
Hawkesworth et al. (2013)	Oral	Bangladesh	kidney: function (2 Types)
Hsu et al. (2013b)	Oral	Taiwan	kidney: neoplastic lesions
Hsu et al. (2013b)	Oral	Taiwan	urinary bladder: neoplastic lesions
Pi et al. (2005)	Oral	China	urine: parameters
Sawada et al. (2013)	Oral	Japan	kidney: neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chiou et al. (2005)	Oral	Taiwan	kidney: function
Enterline and Marsh (1982)	Inhalation	United States	kidney: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	kidney: nonneoplastic lesions (2 Types)
Lewis et al. (1999)	Oral	United States	kidney: neoplastic lesions
Lewis et al. (1999)	Oral	United States	kidney: nonneoplastic lesions
Lubin et al. (1981)	Inhalation	United States	kidney: neoplastic lesions
Yuan et al. (2010)	Oral	Chile	kidney: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (2011a)	Oral	Taiwan	kidney: function (3 Types)
Eom et al. (2011)	Oral	Korea	kidney: function
García-Vargas et al. (1994)	Oral	Mexico	urine: parameters
Hernández-Zavala et al. (1999)	Oral	Mexico	urine: parameters
Jayatilake et al. (2013)	Inhalation	Sri Lanka	kidney: nonneoplastic lesions
Jayatilake et al. (2013)	Oral	Sri Lanka	kidney: nonneoplastic lesions
Ng et al. (2005)	Inhalation	China	urine: parameters
Nordberg et al. (2005)	Inhalation	China	kidney: function
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Buchet and Lison (1998)	Oral	Belgium	kidney: neoplastic lesions
Chen et al. (1985)	Oral	Taiwan	kidney: neoplastic lesions
Chen and Wang (1990)	Oral	Taiwan	kidney: neoplastic lesions
Chen et al. (1992)	Oral	Taiwan	kidney: neoplastic lesions
Chiu and Yang (2005)	Oral	Taiwan	kidney: function
Guo et al. (1997)	Oral	Taiwan	kidney: neoplastic lesions
Guo et al. (1997)	Oral	Taiwan	ureter: neoplastic lesions
Han et al. (2009)	Oral	United States	kidney: neoplastic lesions

Hinwood et al. (1999)	Oral	Australia	kidney: neoplastic lesions
Hopenhayn-Rich et al. (1998)	Oral	Argentina	kidney: neoplastic lesions
Meliker et al. (2007)	Oral	United States	kidney: function
Meliker et al. (2007)	Oral	United States	kidney: neoplastic lesions
Mouly et al. (2012)	Oral	France	kidney: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	kidney: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	kidney: neoplastic lesions
Smith et al. (1998)	Oral	Chile	kidney: neoplastic lesions
Smith et al. (2012)	Oral	Chile	kidney: function
Tsai et al. (1999)	Oral	Taiwan	kidney: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	kidney: nonneoplastic lesions
Wang et al. (2003)	Oral	Taiwan	kidney: function
Wang et al. (2009b)	Oral	China	kidney: function
Wu et al. (1989)	Oral	Taiwan	kidney: neoplastic lesions
Xie et al. (2001)	Inhalation	China	urine: parameters
Yang et al. (2004)	Oral	Taiwan	kidney: neoplastic lesions

3.1.11 Summary of Epidemiology Studies for Hazard Identification for Mortality

Health Effect Category Route of Exposure Study Type	Count
Mortality	**19**
Oral	13
Cohort	8
Ecological	5
Inhalation	6
Cohort	6

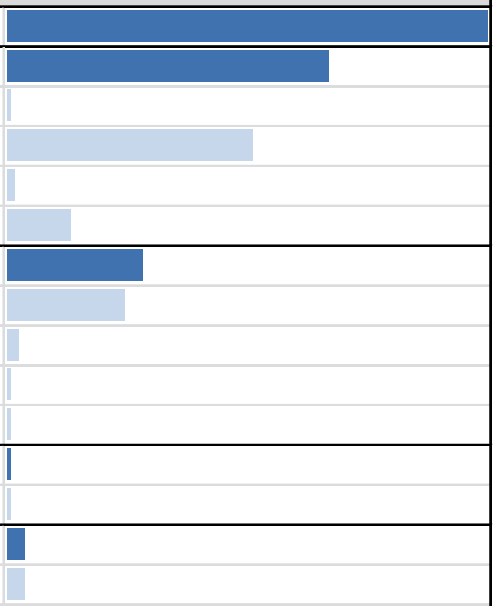


Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Argos et al. (2010)	Oral	Bangladesh	mortality
Rahman et al. (2013)	Oral	Bangladesh	mortality (2 Types)
Sohel et al. (2009)	Oral	Bangladesh	mortality
Sohel et al. (2009)	Oral	Bangladesh	total body neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Enterline and Marsh (1982)	Inhalation	United States	mortality (2 Types)
Lubin et al. (1981)	Inhalation	United States	mortality (2 Types)
Pinto et al. (1978)	Inhalation	United States	mortality
Tsuda et al. (1994)	Oral	Japan	mortality
Tsuda et al. (1995)	Oral	Japan	mortality
Wade et al. (2009)	Oral	China	total body neoplastic lesions
Welch et al. (1982)	Inhalation	United States	mortality
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Brown and Chen (1995)	Oral	Taiwan	mortality
Medrano et al. (2010)	Oral	Spain	mortality
Smith et al. (1998)	Oral	Chile	mortality
Tsai et al. (1999)	Oral	Taiwan	mortality
Tseng (1977)	Oral	Taiwan	mortality

3.1.12 Summary of Epidemiology Studies for Hazard Identification for Nervous System Effects

Health Effect Category Route of Exposure Study Type	Count
Nervous System Effects	**127**
Oral	85
Case-control	1
Cross-sectional	65
Cohort	2
Ecological	17
Inhalation	36
Cross-sectional	31
Cohort	3
Ecological	1
Other	1
Dermal	1
Other	1
Route Unknown	5
Case-control	5



*Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE REPORT			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Kerr (1875)	Inhalation	United Kingdom	clinical observation
Kerr (1875)	Dermal	United Kingdom	clinical observation
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Adams et al. (2013)	Route unknown	United States	CNS: function - behavioral (4 Types)
Ghosh (2013)	Oral	India	PNS: function
Park et al. (2014)	Route unknown	Korea, Republic Of	CNS: function - cognition
COHORT (RETROSPECTIVE)			
Study References	**Route of**	**Country**	**Health Effect**

	Exposure		
Chiou et al. (2005)	Oral	Taiwan	sensory neuropathy
Enterline and Marsh (1982)	Inhalation	United States	eye: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	nervous system: neoplastic lesions
Lewis et al. (1999)	Oral	United States	nervous system: neoplastic lesions
Navas-Acién et al. (2002)	Inhalation	Sweden	brain: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ali et al. (2010)	Oral	Bangladesh	cholinesterase activity
Blom et al. (1985)	Inhalation	Sweden	PNS: function (2 Types)
Chakraborti et al. (2003)	Oral	India	sensory neuropathy
Feldman et al. (1979)	Inhalation	United States	sensory function (3 Types)
Feldman et al. (1979)	Inhalation	United States	sensory neuropathy (2 Types)
Ghosh et al. (2007b)	Oral	India	eye: nonneoplastic lesions
Ghosh et al. (2007b)	Oral	India	sensory neuropathy
Gong et al. (2011)	Oral	United States	CNS: function - cognition
Guo et al. (2007)	Oral	Mongolia	sensory neuropathy (4 Types)
Hafeman et al. (2005)	Oral	Bangladesh	sensory neuropathy (2 Types)
Halatek et al. (2009)	Inhalation	Poland	brain: function (other than FOB) (4 Types)
Kreiss et al. (1983)	Oral	United States	sensory function (10 Types)
Kreiss et al. (1983)	Oral	United States	sensory neuropathy
Lagerkvist and Zetterlund (1994)	Inhalation	Sweden	PNS: function (10 Types)
Li et al. (2006)	Oral	China	sensory neuropathy (4 Types)
Lilis et al. (1985)	Inhalation	Canada	clinical observation
Lin et al. (2008)	Oral	Taiwan	eye: nonneoplastic lesions
Mackenzie and Kyle (1984)	Inhalation	Canada	PNS: function (2 Types)
Mao et al. (2010)	Oral	China	brain: function (other than FOB)
O'Bryant et al. (2011)	Oral	United States	CNS: function - cognition (6 Types)
Otto et al. (2006)	Oral	China	sensory function (4 Types)
Otto et al. (2007)	Oral	China	sensory neuropathy (8 Types)
Paul et al. (2013)	Oral	India	eye: function
Paul et al. (2013)	Oral	India	sensory neuropathy
Rosado et al. (2007)	Oral	Mexico	CNS: function - cognition (11 Types)
See et al. (2007)	Oral	Taiwan	eye: nonneoplastic lesions (4 Types)
Sińczuk-Walczak et al. (2010)	Inhalation	Poland	brain: function (other than FOB) (3 Types)
Sińczuk-Walczak et al. (2010)	Inhalation	Poland	clinical observation (4 Types)
Tseng et al. (2006)	Oral	Taiwan	sensory neuropathy
Zierold et al. (2004)	Oral	United States	CNS: function - behavioral
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**

Ahamed et al. (2006b)	Oral	Bangladesh	sensory neuropathy
Ahamed et al. (2006a)	Oral	India	sensory neuropathy
Buchet and Lison (1998)	Oral	Belgium	nervous system: nonneoplastic lesions
Chakraborti et al. (2013a)	Oral	Bangladesh; India	sensory neuropathy
Gerr et al. (2000)	Inhalation	United States	PNS: function
Rahman et al. (2003)	Oral	India	sensory neuropathy
Tseng (2003)	Oral	Taiwan	sensory function (9 Types)
Valentine et al. (1992)	Oral	United States	clinical observation
Wang et al. (2003)	Oral	Taiwan	eye: nonneoplastic lesions
Wang et al. (2003)	Oral	Taiwan	nervous system: nonneoplastic lesions

3.1.13 Summary of Epidemiology Studies for Hazard Identification for Other Effects

Health Effect Category Route of Exposure Study Type	Count
Other	**42**
Oral	28
Cross-sectional	9
Cohort	7
Ecological	11
Other	1
Inhalation	10
Case-control	1
Cross-sectional	4
Cohort	5
Route Unknown	4
Cross-sectional	4

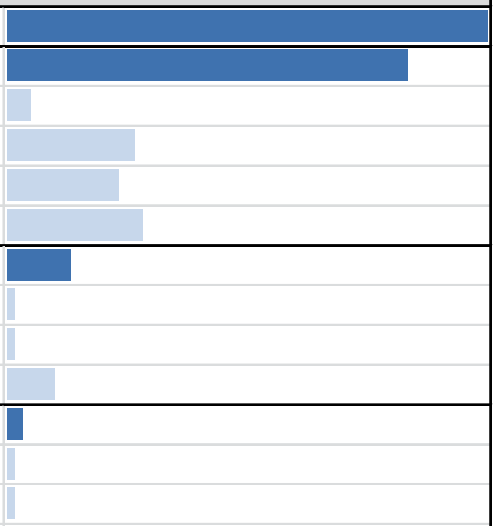
Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE SERIES			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Choprapawon and Porapakkham (2001)	Oral	Thailand	total body neoplastic lesions
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Sobel et al. (1987)	Inhalation	United States	soft tissue: neoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chiou et al. (1995)	Oral	Taiwan	total body neoplastic lesions
Chung et al. (2012)	Oral	Taiwan	total body neoplastic lesions (2 Types)
Enterline et al. (1995)	Inhalation	United States	bone: neoplastic lesions
Hsu et al. (2013b)	Oral	Taiwan	total body neoplastic lesions
Wang et al. (2011a)	Oral	Taiwan	total body neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of**	**Country**	**Health Effect**

	Exposure		
Bulbulyan et al. (1996)	Inhalation	Russia	total body neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	bone: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	total body neoplastic lesions
Nakadaira et al. (2002)	Oral	Japan	total body neoplastic lesions
Pinto et al. (1978)	Inhalation	United States	total body neoplastic lesions
Tsuda et al. (1995)	Oral	Japan	total body neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Akbal et al. (2013)	Route unknown	Turkey	bone: gross pathology (4 Types)
Cordova et al. (2013)	Oral	Mexico	genetic endpoints (2 Types)
Fujino et al. (2004)	Oral	China	brain: function (other than FOB)
Kurttio et al. (1998)	Oral	Finland	clinical observation
Majumdar et al. (2009)	Oral	India	clinical observation
Mazumder et al. (2013)	Oral	India	hair follicle: gross pathology
Mitra et al. (2002)	Oral	Bangladesh	clinical observation
Paul et al. (2013)	Oral	India	bone: neoplastic lesions
Sińczuk-Walczak et al. (2010)	Inhalation	Poland	clinical observation (4 Types)
Syed et al. (2012)	Oral	Bangladesh	CNS: function - behavioral
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Cebrián et al. (1983)	Oral	Mexico	clinical observation
Dastgiri et al. (2010)	Oral	Iran	hair follicle: nonneoplastic lesions
Han et al. (2009)	Oral	United States	total body neoplastic lesions
Mazumder et al. (2009)	Oral	Cambodia	clinical observation
Moore et al. (2002)	Oral	United States	total body neoplastic lesions
Smith et al. (2012)	Oral	Chile	total body neoplastic lesions
Tsai et al. (1998)	Oral	Taiwan	total body neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	bone: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	total body neoplastic lesions
Varsányi et al. (1991)	Oral	Hungary	total body neoplastic lesions
Yorifuji et al. (2011)	Oral	Japan	total body neoplastic lesions

3.1.14 Summary of Epidemiology Studies for Hazard Identification for Reproductive System Effects including Pregnancy Outcomes

Health Effect Category Route of Exposure Study Type	Count
Reproductive System Effects including Pr	**60**
Oral	50
Case-control	3
Cross-sectional	16
Cohort	14
Ecological	17
Inhalation	8
Case-control	1
Cohort	1
Ecological	6
Route Unknown	2
Case-control	1
Cohort	1



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

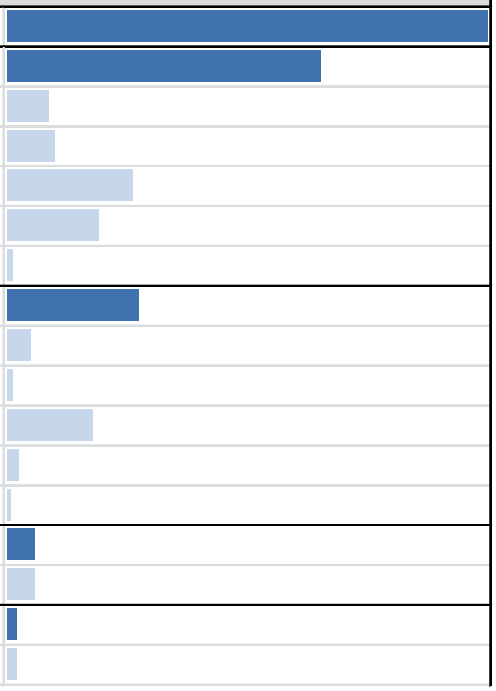
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ihrig et al. (1998)	Inhalation	United States	stillbirth
Sengupta et al. (2013)	Oral	India	sperm parameters (2 Types)
Shen et al. (2013)	Route unknown	China	male reproductive system: nonneoplastic lesions
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Garland et al. (1996)	Oral	United States	mammary gland: neoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Baastrup et al. (2008)	Oral	Denmark	female reproductive system: neoplastic lesions
Baastrup et al. (2008)	Oral	Denmark	male accessory sex gland: neoplastic lesions
García-Esquinas et al. (2013)	Oral	United States	male accessory sex gland:

			neoplastic lesions
García-Esquinas et al. (2013)	Oral	United States	mammary gland: neoplastic lesions
Pollack et al. (2013)	Route unknown	United States	female reproductive system disease/dysfunction
Rahman et al. (2010)	Oral	Bangladesh	spontaneous abortion/miscarriage
Rahman et al. (2010)	Oral	Bangladesh	stillbirth
Sawada et al. (2013)	Oral	Japan	female reproductive system: neoplastic lesions
Sawada et al. (2013)	Oral	Japan	male accessory sex gland: neoplastic lesions
Sawada et al. (2013)	Oral	Japan	mammary gland: neoplastic lesions
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Enterline and Marsh (1982)	Inhalation	United States	testis: neoplastic lesions
Lewis et al. (1999)	Oral	United States	female reproductive system: neoplastic lesions (2 Types)
Lewis et al. (1999)	Oral	United States	male accessory sex gland: neoplastic lesions
Lewis et al. (1999)	Oral	United States	uterus: neoplastic lesions
Tsuda et al. (1995)	Oral	Japan	uterus: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ahmad et al. (2001)	Oral	Bangladesh	postimplantation loss
Chakraborti et al. (2003)	Oral	India	preterm birth/delivery (<37 weeks)
Chakraborti et al. (2003)	Oral	India	stillbirth
Kwok et al. (2006)	Oral	Bangladesh	stillbirth
Milton et al. (2005)	Oral	Bangladesh	spontaneous abortion/miscarriage
Milton et al. (2005)	Oral	Bangladesh	stillbirth
Mukherjee et al. (2005)	Oral	India	preterm birth/delivery (<37 weeks)
Mukherjee et al. (2005)	Oral	India	spontaneous abortion/miscarriage
Mukherjee et al. (2005)	Oral	India	stillbirth
Sen and Chaudhuri (2008)	Oral	India	spontaneous abortion/miscarriage
Sen and Chaudhuri (2008)	Oral	India	stillbirth
Von Ehrenstein et al. (2006)	Oral	India	spontaneous abortion/miscarriage
Von Ehrenstein et al. (2006)	Oral	India	stillbirth
Xu et al. (2012)	Oral	China	sperm parameters (3 Types)
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Aelion et al. (2013)	Inhalation	United States	preterm birth/delivery (<37 weeks)
Ahamed et al. (2006b)	Oral	Bangladesh	preterm birth/delivery (<37 weeks)
Ahamed et al. (2006b)	Oral	Bangladesh	stillbirth

Chakraborti et al. (2013a)	Oral	Bangladesh; India	spontaneous abortion/miscarriage
Chen and Wang (1990)	Oral	Taiwan	male accessory sex gland: neoplastic lesions
Cherry et al. (2008)	Oral	Bangladesh	stillbirth
Hinwood et al. (1999)	Oral	Australia	male reproductive system: neoplastic lesions
Meliker et al. (2007)	Oral	United States	female reproductive system: neoplastic lesions
Myers et al. (2010)	Oral	China	stillbirth
Rivara et al. (1997)	Inhalation	Chile	cervix: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	cervix: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	male accessory sex gland: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	male accessory sex gland: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	mammary gland: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	mammary gland: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	testis: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	testis: neoplastic lesions
Stocks (1960)	Inhalation	England	mammary gland: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	cervix: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	male reproductive system: neoplastic lesions
Wu et al. (1989)	Oral	Taiwan	male accessory sex gland: neoplastic lesions
Yang et al. (2003)	Oral	Taiwan	preterm birth/delivery (<37 weeks)
Yang et al. (2008a)	Oral	Taiwan	male accessory sex gland: neoplastic lesions

3.1.15 Summary of Epidemiology Studies for Hazard Identification for Respiratory Effects

Health Effect Category Route of Exposure Study Type	Count
Respiratory Effects	**158**
Oral	103
Case-control	14
Cross-sectional	16
Cohort	41
Ecological	30
Other	2
Inhalation	43
Case-control	8
Cross-sectional	2
Cohort	28
Ecological	4
Other	1
In Utero	9
Cohort	9
Route Unknown	3
Case-control	3



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE SERIES			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Mazumder (2003)	Oral	India	clinical observation
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Axelson et al. (1978)	Inhalation	Sweden	lung: neoplastic lesions
Chen et al. (1986)	Oral	Taiwan	lung: neoplastic lesions
D'Errico et al. (2009)	Inhalation	Italy	nasal cavity: neoplastic lesions
Dauphiné et al. (2013)	Oral	United States	lung: neoplastic lesions
Ferreccio et al. (1998)	Oral	Chile	lung: neoplastic lesions
Ferreccio et al. (2000)	Oral	Chile	lung: neoplastic lesions
Ferreccio et al. (2013b)	Oral	Chile	lung: neoplastic lesions
Ghosh (2013)	Oral	India	cough

Ghosh (2013)	Oral	India	lung: spirometry
Ghosh (2013)	Oral	India	respiratory system: neoplastic lesions
Ghosh (2013)	Oral	India	respiratory system: nonneoplastic lesions
Grimsrud et al. (2005)	Inhalation	Norway	lung: neoplastic lesions
Heck et al. (2009)	Oral	United States	lung: neoplastic lesions (2 Types)
Hu et al. (1999)	Inhalation	Canada	lung: neoplastic lesions
Khlifi et al. (2014)	Route unknown	Tunisia	larynx: neoplastic lesions
Khlifi et al. (2014)	Route unknown	Tunisia	pharynx: neoplastic lesions
Khlifi et al. (2014)	Route unknown	Tunisia	respiratory system: neoplastic lesions
Mostafa et al. (2008)	Oral	Bangladesh	lung: neoplastic lesions
Steinmaus et al. (2013)	Oral	Chile	lung: neoplastic lesions
'T Mannetje et al. (2011)	Inhalation	Central/Eastern Europe and UK	lung: neoplastic lesions
Taylor et al. (1989)	Inhalation	China	lung: neoplastic lesions
Wadhwa et al. (2011b)	Oral	Pakistan	lung: neoplastic lesions
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ades and Kazantzis (1988)	Inhalation	FRANCE	lung: neoplastic lesions
Lee-Feldstein (1989)	Inhalation	United States	lung: neoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Baastrup et al. (2008)	Oral	Denmark	respiratory system: neoplastic lesions
Chen et al. (2004a)	Oral	Taiwan	lung: neoplastic lesions
Chen et al. (2010a)	Oral	Taiwan	lung: neoplastic lesions (6 Types)
Chiou et al. (1995)	Oral	Taiwan	lung: neoplastic lesions
Chung et al. (2012)	Oral	Taiwan	lung: neoplastic lesions
Enterline et al. (1995)	Inhalation	United States	lung: neoplastic lesions
Farzan et al. (2013)	In utero	United States	respiratory system: nonneoplastic lesions (7 Types)
García-Esquinas et al. (2013)	Oral	United States	lung: neoplastic lesions
Hsu et al. (2013a)	Oral	Taiwan	lung: neoplastic lesions
Hsu et al. (2013b)	Oral	Taiwan	lung: neoplastic lesions
Mazumdar et al. (1989)	Inhalation	United States	lung: neoplastic lesions
Parvez et al. (2013)	Oral	Bangladesh	lung: function (2 Types)
Parvez et al. (2010)	Oral	Bangladesh	clinical observation (3 Types)

Rahman et al. (2011)	Oral	Bangladesh	cough (2 Types)
Rahman et al. (2011)	In utero	Bangladesh	cough (2 Types)
Raqib et al. (2009)	Oral	Bangladesh	lung: function
Sawada et al. (2013)	Oral	Japan	lung: neoplastic lesions
Smith et al. (2013)	Oral	Bangladesh	lung: function (8 Types)
COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Bulbulyan et al. (1996)	Inhalation	Russia	lung: neoplastic lesions
Dauphiné et al. (2011)	Oral	Chile	lung: function (5 Types)
Enterline and Marsh (1982)	Inhalation	United States	larynx: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	lung: function (4 Types)
Enterline and Marsh (1982)	Inhalation	United States	lung: neoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	lung: nonneoplastic lesions
Enterline and Marsh (1982)	Inhalation	United States	respiratory system: neoplastic lesions
Enterline et al. (1987)	Inhalation	United States	lung: neoplastic lesions
Jarup et al. (1989)	Inhalation	Sweden	lung: neoplastic lesions
Lewis et al. (1999)	Oral	United States	airway obstruction
Lewis et al. (1999)	Oral	United States	respiratory system: neoplastic lesions
Lewis et al. (1999)	Oral	United States	respiratory system: nonneoplastic lesions
Lubin et al. (1981)	Inhalation	United States	larynx: neoplastic lesions (2 Types)
Lubin et al. (1981)	Inhalation	United States	lung: function (3 Types)
Lubin et al. (1981)	Inhalation	United States	lung: neoplastic lesions
Lubin et al. (1981)	Inhalation	United States	respiratory system: neoplastic lesions (2 Types)
Lubin et al. (2000)	Inhalation	United States	respiratory system: neoplastic lesions
Lubin et al. (2008)	Inhalation	United States	respiratory system: neoplastic lesions
Nakadaira et al. (2002)	Oral	Japan	lung: neoplastic lesions
Pinto et al. (1978)	Inhalation	United States	lung: function
Pinto et al. (1978)	Inhalation	United States	respiratory system: neoplastic lesions
Smith et al. (2011)	Oral	Chile	lung: function
Sorahan (2009)	Inhalation	United States	lung: neoplastic lesions
Tsuda et al. (1995)	Oral	Japan	lung: neoplastic lesions
Welch et al. (1982)	Inhalation	United States	lung: neoplastic lesions
Welch et al. (1982)	Inhalation	United States	respiratory system: nonneoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of**	**Country**	**Health Effect**

	Exposure		
Chakraborti et al. (2013b)	Oral	India	bronchitis
Chattopadhyay et al. (2010)	Oral	India	lung: spirometry
De et al. (2004)	Oral	India	lung: spirometry
Ghosh et al. (2007b)	Oral	India	lung: function
Guo et al. (2007)	Oral	Mongolia	lung: function
Halatek et al. (2009)	Inhalation	Poland	clara cell protein (CC16)
Halatek et al. (2009)	Inhalation	Poland	lung: spirometry
Majumdar et al. (2009)	Oral	India	lung: nonneoplastic lesions
Mazumder et al. (2005)	Oral	India	lung: nonneoplastic lesions
Milton et al. (2001)	Oral	Bangladesh	respiratory system: nonneoplastic lesions
Nafees et al. (2011)	Oral	Pakistan	lung: function (3 Types)
Parvez et al. (2008)	Oral	Bangladesh	lung: spirometry (3 Types)
Paul et al. (2013)	Oral	India	lung: function
Paul et al. (2013)	Oral	India	lung: neoplastic lesions
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Buchet and Lison (1998)	Oral	Belgium	lung: neoplastic lesions
Chen et al. (1985)	Oral	Taiwan	lung: neoplastic lesions
Chen and Wang (1990)	Oral	Taiwan	lung: neoplastic lesions
Chen and Wang (1990)	Oral	Taiwan	nasal cavity: neoplastic lesions
Chen et al. (1992)	Oral	Taiwan	lung: neoplastic lesions
Chiu et al. (2004)	Oral	Taiwan	lung: neoplastic lesions
Engel and Smith (1994)	Oral	United States	lung: function
Engel and Smith (1994)	Oral	United States	lung: neoplastic lesions
Guo (2004)	Oral	Taiwan	lung: neoplastic lesions
Guo et al. (2004)	Oral	Taiwan	lung: neoplastic lesions
Han et al. (2009)	Oral	United States	lung: neoplastic lesions
Hinwood et al. (1999)	Oral	Australia	respiratory system: neoplastic lesions
Hopenhayn-Rich et al. (1998)	Oral	Argentina	lung: neoplastic lesions
Marshall et al. (2007)	Oral	Chile	lung: neoplastic lesions
Meliker et al. (2007)	Oral	United States	lung: function
Meliker et al. (2007)	Oral	United States	respiratory system: neoplastic lesions
Morales et al. (2000)	Oral	Taiwan	lung: neoplastic lesions
Mouly et al. (2012)	Oral	France	lung: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	larynx: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	larynx: neoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	lung: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	lung: neoplastic lesions
Smith et al. (1998)	Oral	Chile	airway obstruction

Smith et al. (1998)	Oral	Chile	lung: neoplastic lesions
Smith et al. (2006)	Oral	Chile	lung: function
Smith et al. (2006)	Oral	Chile	lung: neoplastic lesions
Smith et al. (2012)	Oral	Chile	larynx: neoplastic lesions
Stocks (1960)	Inhalation	England	clinical observation
Stocks (1960)	Inhalation	England	lung: neoplastic lesions
Su et al. (2011)	Oral	Taiwan	lung: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	airway obstruction
Tsai et al. (1999)	Oral	Taiwan	respiratory system: neoplastic lesions
Wu et al. (1989)	Oral	Taiwan	lung: neoplastic lesions
Yorifuji et al. (2011)	Oral	Japan	lung: neoplastic lesions
OTHER			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Begum et al. (2012)	Oral	United States, Taiwan, Bangladesh, West Bengal, Inner Mongolia, and China	lung: neoplastic lesions
Pinto et al. (1977)	Inhalation	United States	respiratory system: neoplastic lesions

3.1.16 Summary of Epidemiology Studies for Hazard Identification for Skin Diseases

Health Effect Category Route of Exposure Study Type	Count
Skin Diseases	**156**
Oral	144
Case-control	28
Cross-sectional	56
Cohort	15
Ecological	37
Other	8
Inhalation	10
Case-control	3
Cross-sectional	2
Cohort	2
Ecological	3
Dermal	1
Ecological	1
Route Unknown	1
Ecological	1

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CASE REPORT			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Zaldívar et al. (1981)	Oral	Chile	skin and subcutaneous tissue: neoplastic lesions
CASE SERIES			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Cabrera and Gomez (2003)	Oral	Argentina	skin and subcutaneous tissue: neoplastic lesions
Cabrera and Gomez (2003)	Oral	Argentina	skin and subcutaneous tissue: nonneoplastic lesions
Choprapawon and Porapakkham (2001)	Oral	Thailand	skin and subcutaneous tissue: neoplastic lesions
Dhar et al. (1997)	Oral	Bangladesh	skin and subcutaneous tissue: neoplastic lesions

Mazumder (2003)	Oral	India	skin and subcutaneous tissue: neoplastic lesions
Mazumder (2003)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Yeh et al. (1968)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
CASE-CONTROL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Applebaum et al. (2007)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions
Beane Freeman et al. (2004)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions
Bhowmick et al. (2013)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Breton et al. (2006)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Chen et al. (2003a)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Ghosh (2013)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions (3 Types)
Gilbert-Diamond et al. (2013)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions
Graham et al. (1961)	Oral	United States	skin and subcutaneous tissue: nonneoplastic lesions
Guo et al. (2006b)	Oral	Inner Mongolia	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Hon et al. (2012)	Oral	China	skin and subcutaneous tissue: nonneoplastic lesions
Karagas et al. (2001)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions (2 Types)
Karagas et al. (2002)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions
Leonardi et al. (2012)	Oral	Hungary, Romania, Slovakia	skin and subcutaneous tissue: neoplastic lesions
Lindberg et al. (2010)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
McCarty et al. (2006)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
McDonald et al. (2007)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Pesch et al. (2002)	Inhalation	Slovakia	skin and subcutaneous tissue: neoplastic lesions
Rahman et al. (2006b)	Oral	Bangladesh	skin and subcutaneous tissue:

			nonneoplastic lesions
Rahman et al. (2006a)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Ranft et al. (2003)	Inhalation	Slovakia	skin and subcutaneous tissue: neoplastic lesions
Ranft et al. (2003)	Oral	Slovakia	skin and subcutaneous tissue: neoplastic lesions
Rosales-Castillo et al. (2004)	Oral	Mexico	skin and subcutaneous tissue: neoplastic lesions
Surdu et al. (2013)	Inhalation	Hungary, Romania, Slovakia	skin and subcutaneous tissue: neoplastic lesions
CASE-CONTROL (NESTED)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Chen et al. (2007c)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Hall et al. (2006)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Haque et al. (2003)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Lindberg et al. (2008)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
COHORT (PROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Argos et al. (2011)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Baastrup et al. (2008)	Oral	Denmark	skin and subcutaneous tissue: neoplastic lesions (2 Types)
Hsu et al. (2013a)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions (2 Types)
Hsu et al. (2013a)	Oral	Taiwan	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Hsueh et al. (1997)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Melkonian et al. (2011)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Pierce et al. (2011)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Seow et al. (2012)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Valentine et al. (1991)	Oral	United States	skin and subcutaneous tissue: nonneoplastic lesions

COHORT (RETROSPECTIVE)			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Enterline and Marsh (1982)	Inhalation	United States	skin and subcutaneous tissue: neoplastic lesions
Lewis et al. (1999)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions
Lubin et al. (1981)	Inhalation	United States	skin and subcutaneous tissue: neoplastic lesions
CROSS-SECTIONAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ahmad et al. (1999)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Ahsan et al. (2000)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions (3 Types)
Ahsan et al. (2006)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Argos et al. (2007)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Barati et al. (2010)	Oral	Iran	skin and subcutaneous tissue: nonneoplastic lesions (6 Types)
Borgono et al. (1977)	Oral	Chile	skin and subcutaneous tissue: nonneoplastic lesions
Chakraborti et al. (2013b)	Oral	India	skin and subcutaneous tissue: neoplastic lesions
Chakraborti et al. (2013b)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions (5 Types)
Chakraborti et al. (2003)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Chen et al. (2006a)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Fatmi et al. (2009)	Oral	Pakistan	skin and subcutaneous tissue: nonneoplastic lesions
Fatmi et al. (2013)	Oral	Pakistan	skin and subcutaneous tissue: nonneoplastic lesions
Ghosh et al. (2007b)	Oral	India	skin and subcutaneous tissue: neoplastic lesions
Ghosh et al. (2007b)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Guo et al. (2006a)	Oral	China	skin and subcutaneous tissue: nonneoplastic lesions
Guo et al. (2007)	Oral	Mongolia	skin and subcutaneous tissue: nonneoplastic lesions
Hashim et al. (2013)	Oral	Cambodia	skin and subcutaneous tissue:

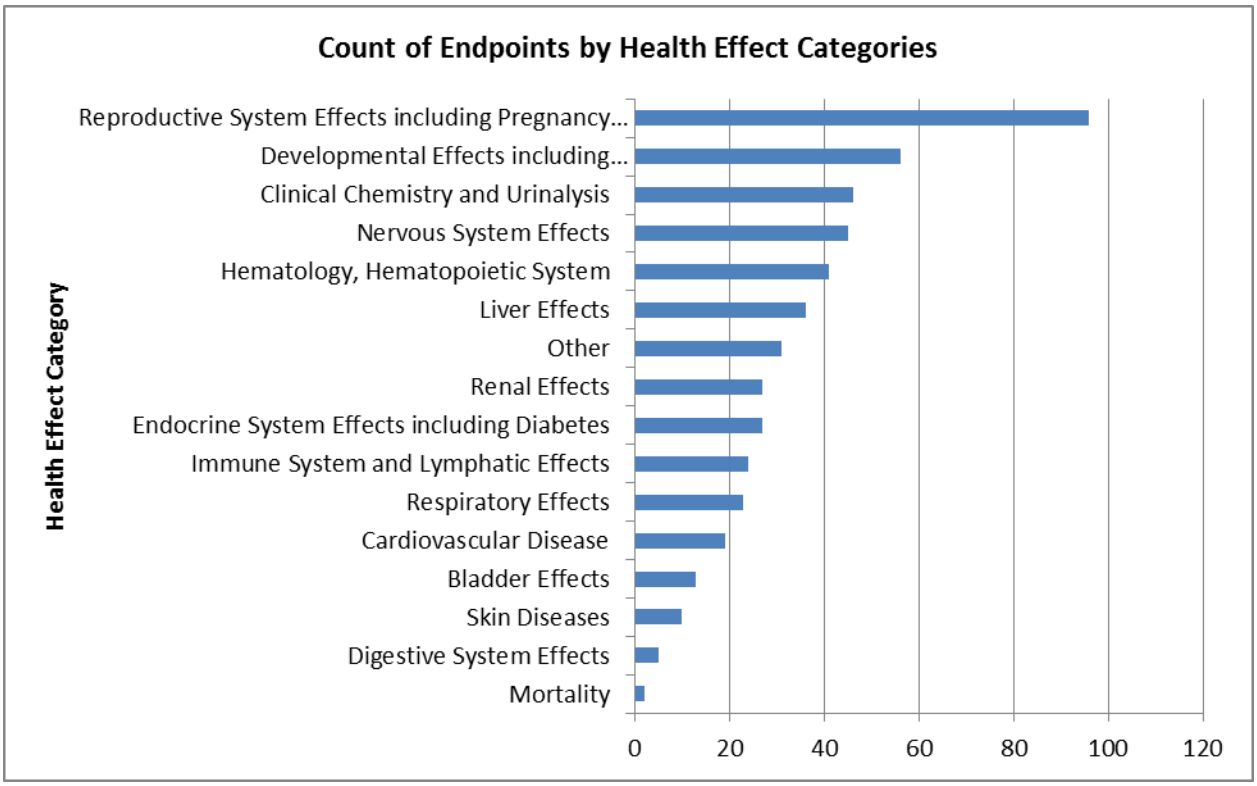
			nonneoplastic lesions (4 Types)
Hsueh et al. (1995)	Oral	Taiwan	skin and subcutaneous tissue: nonneoplastic lesions
Knobeloch et al. (2006)	Oral	United States	soft tissue: neoplastic lesions
Lamm et al. (2007)	Oral	China	skin and subcutaneous tissue: neoplastic lesions
Lamm et al. (2007)	Oral	China	skin and subcutaneous tissue: nonneoplastic lesions
Li et al. (2013a)	Oral	China	skin and subcutaneous tissue: neoplastic lesions
Liu et al. (2013)	Oral	China	skin and subcutaneous tissue: nonneoplastic lesions
Maden et al. (2011)	Oral	Nepal	skin and subcutaneous tissue: nonneoplastic lesions
Maharjan et al. (2005)	Oral	Nepal	skin and subcutaneous tissue: nonneoplastic lesions
Maharjan et al. (2007)	Oral	Nepal	skin and subcutaneous tissue: nonneoplastic lesions
Mazumder et al. (1998)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Mazumder et al. (2013)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Mitra et al. (2002)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Mosaferi et al. (2008)	Oral	Iran	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Paul et al. (2013)	Oral	India	skin and subcutaneous tissue: neoplastic lesions
Pavittranon et al. (2003)	Oral	Thailand	skin and subcutaneous tissue: nonneoplastic lesions
Pei et al. (2013)	Oral	China	skin and subcutaneous tissue: nonneoplastic lesions
Perry et al. (1948)	Inhalation	Not Specified	skin and subcutaneous tissue: nonneoplastic lesions
Pesola et al. (2012)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Schäfer et al. (1999)	Inhalation	Germany	skin and subcutaneous tissue: nonneoplastic lesions
Smith et al. (2000)	Oral	Chile	skin and subcutaneous tissue: nonneoplastic lesions
Tondel et al. (1999)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Valenzuela et al. (2005)	Oral	Mexico	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Xia et al. (2009)	Oral	China	skin and subcutaneous tissue:

			nonneoplastic lesions
ECOLOGICAL			
Study References	**Route of Exposure**	**Country**	**Health Effect**
Ahamed et al. (2006b)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Ahamed et al. (2006a)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Bencko et al. (2009)	Inhalation	Slovakia	skin and subcutaneous tissue: neoplastic lesions
Besuschio et al. (1980)	Oral	Argentina	skin and subcutaneous tissue: neoplastic lesions
Biswas et al. (1998)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Brown et al. (1989)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Cebrián et al. (1983)	Oral	Mexico	skin and subcutaneous tissue: nonneoplastic lesions
Chakraborti et al. (2013a)	Oral	Bangladesh; India	skin and subcutaneous tissue: nonneoplastic lesions
Chen et al. (1985)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Chen and Wang (1990)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Del Razo et al. (1997)	Oral	Mexico	skin and subcutaneous tissue: nonneoplastic lesions
Guo et al. (1998)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Guo et al. (2001)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Hinwood et al. (1999)	Oral	Australia	skin and subcutaneous tissue: neoplastic lesions
Hopenhayn-Rich et al. (1998)	Oral	Argentina	skin and subcutaneous tissue: neoplastic lesions
Maharjan et al. (2006)	Oral	Nepal	skin and subcutaneous tissue: nonneoplastic lesions
Mazumder et al. (2009)	Oral	Cambodia	skin and subcutaneous tissue: nonneoplastic lesions
Mazumder et al. (2010)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Mcdonald et al. (2006)	Oral	Bangladesh	skin and subcutaneous tissue: nonneoplastic lesions
Morton et al. (1976)	Oral	United States	skin and subcutaneous tissue: neoplastic lesions
Mouly et al. (2012)	Oral	France	skin and subcutaneous tissue:

			neoplastic lesions
Philipp et al. (1983)	Inhalation	United Kingdom	skin and subcutaneous tissue: neoplastic lesions
Philipp et al. (1983)	Oral	United Kingdom	skin and subcutaneous tissue: neoplastic lesions
Philipp et al. (1983)	Dermal	United Kingdom	skin and subcutaneous tissue: neoplastic lesions
Rahman et al. (2003)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Rahman et al. (2005c)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Rahman et al. (2005a)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Rahman et al. (2005b)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Rivara et al. (1997)	Inhalation	Chile	skin and subcutaneous tissue: neoplastic lesions
Rivara et al. (1997)	Oral	Chile	skin and subcutaneous tissue: neoplastic lesions
Saha and Poddar (1986)	Oral	India	skin and subcutaneous tissue: nonneoplastic lesions
Smith et al. (1998)	Oral	Chile	skin and subcutaneous tissue: neoplastic lesions
Tsai et al. (1999)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Tseng et al. (1968)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions (2 Types)
Tseng (1977)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Valentine et al. (1992)	Oral	United States	clinical observation
Valentine et al. (1992)	Oral	United States	skin and subcutaneous tissue: nonneoplastic lesions
Wheeler et al. (2013)	Route unknown	United Kingdom	skin and subcutaneous tissue: neoplastic lesions
Wu et al. (1989)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Yeh (1973)	Oral	Taiwan	skin and subcutaneous tissue: neoplastic lesions
Yu et al. (2007)	Oral	China	skin and subcutaneous tissue: nonneoplastic lesions

3.2 Summary of Toxicology Literature Identified to Support Hazard Identification for Inorganic Arsenic

3.2.1 Overview of Toxicology Studies Identified



3.2.2 Summary of Toxicology Studies for Hazard Identification for Bladder Effects

Health Effect Category Route of Exposure Study Type	Count
Bladder Effects	**12**
Oral	10
Chronic (>90 days)	2
Reproductive/Developmental	8
Inhalation	2
Subchronic (30 days to < 90 days)	2

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Nain and Smits (2012)	Oral	rat	urinary bladder: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	urinary bladder: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Tokar et al. (2010b)	Oral	mice	urinary bladder: neoplastic lesions (4 Types)
Tokar et al. (2010b)	Oral	mice	urinary bladder: nonneoplastic lesions (2 Types)
Tokar et al. (2011)	Oral	mice	urinary bladder: nonneoplastic lesions (2 Types)
Tokar et al. (2012)	Oral	mice	urinary bladder: neoplastic lesions
Tokar et al. (2012)	Oral	mice	urinary bladder: nonneoplastic lesions
Waalkes et al. (2006a)	Oral	mice	urinary bladder: nonneoplastic lesions (2 Types)
Waalkes et al. (2006b)	Oral	mice	urinary bladder: neoplastic lesions
Waalkes et al. (2006b)	Oral	mice	urinary bladder: nonneoplastic lesions

SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	urinary bladder: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	urinary bladder: nonneoplastic lesions

3.2.3 Summary of Toxicology Studies for Hazard Identification for Cardiovascular Disease

Health Effect Category Route of Exposure Study Type	Count
Cardiovascular Disease	**19**
Oral	17
Chronic (>90 days)	11
Subchronic (30 days to < 90 days)	5
Reproductive/Developmental	1
Inhalation	2
Subchronic (30 days to < 90 days)	2

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Bunderson et al. (2004)	Oral	mice	inflammatory markers
Bunderson et al. (2004)	Oral	mice	vascular: nonneoplastic lesions (2 Types)
Nain and Smits (2012)	Oral	rat	vascular: nonneoplastic lesions
Sanchez-Soria et al. (2012)	Oral	mice	blood pressure: diastolic
Sanchez-Soria et al. (2012)	Oral	mice	blood pressure: systolic
Sanchez-Soria et al. (2012)	Oral	mice	cardiovascular system: nonneoplastic lesions
Sanchez-Soria et al. (2012)	Oral	mice	heart: relative weight
Simeonova et al. (2003)	Oral	mice	vascular: nonneoplastic lesions (2 Types)

Soucy et al. (2005)	Oral	mice	vascular: gross pathology (2 Types)
Srivastava et al. (2009)	Oral	mice	heart: nonneoplastic lesions (2 Types)
Stępnik et al. (2009)	Oral	mice	heart: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Rogers et al. (2014)	Oral	rat	blood pressure: systolic (2 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	cardiovascular system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	cardiovascular system: nonneoplastic lesions
Lemaire et al. (2011)	Oral	mice	cardiovascular system: nonneoplastic lesions
Lemaire et al. (2011)	Oral	mice	vascular: nonneoplastic lesions
Sharma and Sharma (2013)	Oral	rat	vascular: function
Soucy et al. (2005)	Oral	mice	vascular: gross pathology (4 Types)
Srivastava et al. (2009)	Oral	mice	heart: nonneoplastic lesions

3.2.4 Summary of Toxicology Studies for Hazard Identification for Clinical Chemistry and Urinalysis

Health Effect Category Route of Exposure Study Type	Count
Clinical Chemistry and Urinalysis	**47**
Oral	45
Chronic (>90 days)	23
Subchronic (30 days to < 90 days)	13
Reproductive/Developmental	9
Inhalation	2
Subchronic (30 days to < 90 days)	2

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Das et al. (2012b)	Oral	goat	clinical chemistry, unspecified (3 Types)
Arteel et al. (2008)	Oral	mice	clinical chemistry, unspecified
Dwivedi and Flora (2011)	Oral	rat	alanine aminotransferase (ALT)
Dwivedi and Flora (2011)	Oral	rat	aspartate aminotransferase (AST)
Liu et al. (2000)	Oral	mice	clinical chemistry, unspecified (2 Types)
Nain and Smits (2012)	Oral	rat	alanine aminotransferase (ALT)
Nain and Smits (2012)	Oral	rat	alkaline phosphatase (ALP)
Nain and Smits (2012)	Oral	rat	aspartate aminotransferase (AST)
Nain and Smits (2012)	Oral	rat	blood urea nitrogen (BUN)
Nain and Smits (2012)	Oral	rat	blood: glucose
Nain and Smits (2012)	Oral	rat	chloride
Nain and Smits (2012)	Oral	rat	creatine kinase
Nain and Smits (2012)	Oral	rat	creatinine
Nain and Smits (2012)	Oral	rat	gamma-glutamyl transpeptidase (GGT) (2 Types)
Nain and Smits (2012)	Oral	rat	potassium
Nain and Smits (2012)	Oral	rat	sodium
Nain and Smits (2012)	Oral	rat	total protein
Simeonova et al. (2003)	Oral	mice	clinical chemistry, unspecified (2 Types)

Srivastava et al. (2009)	Oral	mice	cholesterol (2 Types)
Srivastava et al. (2009)	Oral	mice	triglycerides (2 Types)
Wang et al. (2009b)	Oral	rat	blood: glucose
Wang et al. (2009b)	Oral	rat	N-acetyl-beta-D-glucosaminidase (NAG)
Wu et al. (2004)	Oral	mice	urine: parameters
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Rogers et al. (2014)	Oral	rat	clinical chemistry, unspecified
Ahmad et al. (2013)	Oral	mice	clinical chemistry, unspecified
Antonio Garcia et al. (2013)	Oral	rat	clinical chemistry, unspecified
Dávila-Esqueda et al. (2011)	Oral	rat	cholesterol (2 Types)
Dávila-Esqueda et al. (2011)	Oral	rat	clinical chemistry, unspecified
Dávila-Esqueda et al. (2011)	Oral	rat	triglycerides
Srivastava et al. (2007)	Oral	mice	cholesterol
Srivastava et al. (2007)	Oral	mice	clinical chemistry, unspecified
Srivastava et al. (2007)	Oral	mice	triglycerides
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	rat	clinical chemistry, unspecified
Blair et al. (1990b)	Inhalation	mice	clinical chemistry, unspecified
Fouad et al. (2012)	Oral	mice	alanine aminotransferase (ALT)
Owumi et al. (2013)	Oral	rat	clinical chemistry, unspecified
Patra et al. (2012)	Oral	goat	alanine aminotransferase (ALT)
Patra et al. (2012)	Oral	goat	aspartate aminotransferase (AST)
Kharroubi et al. (2014)	Oral	rat	alanine aminotransferase (ALT)
Kharroubi et al. (2014)	Oral	rat	alkaline phosphatase (ALP)
Kharroubi et al. (2014)	Oral	rat	aspartate aminotransferase (AST)
Kharroubi et al. (2014)	Oral	rat	clinical chemistry, unspecified
Lemaire et al. (2011)	Oral	mice	clinical chemistry, unspecified
Majhi et al. (2011)	Oral	rat	clinical chemistry, unspecified (2 Types)
Sharma and Sharma (2013)	Oral	rat	clinical chemistry, unspecified
Srivastava et al. (2009)	Oral	mice	cholesterol
Srivastava et al. (2009)	Oral	mice	triglycerides

3.2.5 Summary of Toxicology Studies for Hazard Identification for Developmental Effects including Neurodevelopmental

Health Effect Category Route of Exposure Study Type	Count
Developmental Effects including Neurod	**61**
Oral	58
Subchronic (30 days to < 90 days)	2
Reproductive/Developmental	56
Inhalation	3
Reproductive/Developmental	3

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Nagymajtenyi et al. (1985)	Inhalation	mice	fetal body weight (2 Types)
Nagymajtenyi et al. (1985)	Inhalation	mice	number of dead fetuses
Nagymajtenyi et al. (1985)	Inhalation	mice	skeletal variation, malformation, or anomaly
Aggarwal et al. (2007)	Oral	rat	crown-rump length
Aggarwal et al. (2007)	Oral	rat	external malformation
Aggarwal et al. (2007)	Oral	rat	fetal body weight
Aggarwal et al. (2007)	Oral	rat	skeletal variation, malformation, or anomaly
Aggarwal et al. (2007)	Oral	rat	soft-tissue variation, malformation, or anomaly
Colomina et al. (1997)	Oral	mice	developmental milestone (2 Types)
Colomina et al. (1997)	Oral	mice	functional observation battery/neuro-behavioral (7 Types)
Gandhi et al. (2012)	Oral	rat	developmental milestone
Gandhi et al. (2012)	Oral	rat	external malformation
Gandhi et al. (2012)	Oral	rat	functional observation battery/neuro-behavioral
Gandhi et al. (2012)	Oral	rat	motor activity
Gandhi et al. (2012)	Oral	rat	reflex ontogeny (9 Types)
Miyazaki et al. (2005)	Oral	mice	fetal body weight
Reilly et al. (2013)	Oral	rat	day at vaginal opening
Rogers et al. (2014)	Oral	rat	birth weight (2 Types)

Ahmad et al. (2013)	Oral	mice	developmental milestone
Ahmad et al. (2013)	Oral	mice	functional observation battery/neuro-behavioral (9 Types)
Antonio Garcia et al. (2013)	Oral	rat	body weight
Antonio Garcia et al. (2013)	Oral	rat	crown-rump length
Chattopadhyay et al. (2002)	Oral	rat	brain: gross pathology
Chattopadhyay et al. (2002)	Oral	rat	motor activity
Chattopadhyay et al. (2002)	Oral	rat	number of dead fetuses
Cronican et al. (2013)	Oral	mice	birth weight
Cronican et al. (2013)	Oral	mice	external malformation
He et al. (2007)	Oral	mice	litter weight (2 Types)
He et al. (2007)	Oral	mice	postnatal body weight
He et al. (2007)	Oral	mice	soft-tissue variation, malformation, or anomaly
Herrera et al. (2013)	Oral	rat	brain: absolute weight
Herrera et al. (2013)	Oral	rat	brain: relative weight
Herrera et al. (2013)	Oral	rat	postnatal body weight
Luo et al. (2013)	Oral	rat	brain: nonneoplastic lesions
Luo et al. (2013)	Oral	rat	functional observation battery/neuro-behavioral
Markowski et al. (2012)	Oral	mice	anogenital distance (2 Types)
Markowski et al. (2012)	Oral	mice	body weight gain (2 Types)
Markowski et al. (2012)	Oral	mice	crown-rump length (2 Types)
Markowski et al. (2012)	Oral	mice	developmental milestone (6 Types)
Markowski et al. (2012)	Oral	mice	functional observation battery/neuro-behavioral (9 Types)
Markowski et al. (2012)	Oral	mice	motor activity (2 Types)
Markowski et al. (2012)	Oral	mice	onset of puberty (2 Types)
Martinez et al. (2008)	Oral	mice	functional observation battery/neuro-behavioral (3 Types)
Martinez-Finley et al. (2009)	Oral	mice	brain: absolute weight
Martinez-Finley et al. (2009)	Oral	mice	functional observation battery/neuro-behavioral (2 Types)
Ramsey et al. (2013a)	Oral	mice	birth weight (2 Types)
Ramsey et al. (2013c)	Oral	mice	birth length
Ramsey et al. (2013c)	Oral	mice	birth weight
Ríos et al. (2009)	Oral	rat	brain: nonneoplastic lesions
Rodríguez et al. (2002)	Oral	rat	body weight
Rodríguez et al. (2002)	Oral	rat	CNS: function - cognition (4 Types)
Rodríguez et al. (2002)	Oral	rat	developmental milestone (6 Types)
Rodríguez et al. (2002)	Oral	rat	locomotor activity (2 Types)
Rodríguez et al. (2002)	Oral	rat	motor activity (2 Types)
Rodríguez et al. (2002)	Oral	rat	postnatal body weight
Xi et al. (2009)	Oral	rat	CNS: function - cognition (7 Types)

Xi et al. (2009)	Oral	rat	developmental milestone (12 Types)
Xi et al. (2009)	Oral	rat	locomotor activity
Xi et al. (2009)	Oral	rat	postnatal body weight
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Nagaraja and Desiraju (1993)	Oral	rat	brain: absolute weight
Nagaraja and Desiraju (1993)	Oral	rat	developmental milestone

3.2.6 Summary of Toxicology Studies for Hazard Identification for Digestive System Effects

Health Effect Category Route of Exposure Study Type	Count
Digestive System Effects	**5**
Oral	3
Chronic (>90 days)	1
Reproductive/Developmental	2
Inhalation	2
Subchronic (30 days to < 90 days)	2

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Stępnik et al. (2009)	Oral	mice	digestive system: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Tokar et al. (2011)	Oral	mice	digestive system: neoplastic lesions (8 Types)
Tokar et al. (2011)	Oral	mice	digestive system: nonneoplastic lesions (2 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of**	**Species**	**Health Effect**

	Exposure		
Blair et al. (1990b)	Inhalation	mice	pancreas: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	pancreas: nonneoplastic lesions

3.2.7 Summary of Toxicology Studies for Hazard Identification for Endocrine System Effects including Diabetes

Health Effect Category Route of Exposure Study Type	Count
Endocrine System Effects including Diabe	**28**
Oral	26
Chronic (>90 days)	2
Subchronic (30 days to < 90 days)	2
Reproductive/Developmental	22
Inhalation	2
Subchronic (30 days to < 90 days)	2

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Nain and Smits (2012)	Oral	rat	thyroid gland: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	endocrine system: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Reilly et al. (2013)	Oral	rat	estrogen
Reilly et al. (2013)	Oral	rat	estrous cyclicity
Reilly et al. (2013)	Oral	rat	growth hormone
Reilly et al. (2013)	Oral	rat	luteinizing hormone (LH)
Dávila-Esqueda et al. (2012)	Oral	rat	adrenal gland: absolute weight
Dávila-Esqueda et al. (2012)	Oral	rat	adrenal gland: nonneoplastic lesions
Dávila-Esqueda et al. (2011)	Oral	rat	blood: glucose (4 Types)
Dávila-Esqueda et al. (2011)	Oral	rat	hematology, unspecified (5 Types)
Dávila-Esqueda et al. (2011)	Oral	rat	pancreas: nonneoplastic lesions (2

			Types)
Goggin et al. (2012)	Oral	mice	glucocorticoids
Martinez et al. (2008)	Oral	mice	corticosterone
Tokar et al. (2010b)	Oral	mice	adrenal gland: neoplastic lesions (2 Types)
Tokar et al. (2010b)	Oral	mice	adrenal gland: nonneoplastic lesions
Tokar et al. (2011)	Oral	mice	adrenal gland: neoplastic lesions (2 Types)
Tokar et al. (2012)	Oral	mice	adrenal gland: neoplastic lesions
Waalkes et al. (2004b)	Oral	mice	adrenal gland: neoplastic lesions (3 Types)
Waalkes et al. (2006a)	Oral	mice	adrenal gland: neoplastic lesions
Waalkes et al. (2006a)	Oral	mice	thyroid gland: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	adrenal gland: neoplastic lesions
Waalkes et al. (2006b)	Oral	mice	thyroid gland: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	adrenal gland: neoplastic lesions (3 Types)
Waalkes et al. (2003)	Oral	mice	thyroid gland: neoplastic lesions (2 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	endocrine system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	endocrine system: nonneoplastic lesions
Paul et al. (2007)	Oral	mice	blood: glucose
Yen et al. (2007)	Oral	mice	pancreas: nonneoplastic lesions

3.2.8 Summary of Toxicology Studies for Hazard Identification for Hematology, Hematopoietic System

Health Effect Category Route of Exposure Study Type	Count
Hematology, Hematopoietic System	**39**
Oral	26
Chronic (>90 days)	12
Subchronic (30 days to < 90 days)	5
Reproductive/Developmental	9
Inhalation	13
Subchronic (30 days to < 90 days)	13

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Ghatak et al. (2011)	Oral	mice	hematology, unspecified (2 Types)
Dwivedi and Flora (2011)	Oral	rat	erythrocyte count
Dwivedi and Flora (2011)	Oral	rat	hematocrit (packed cell volume)
Dwivedi and Flora (2011)	Oral	rat	hemoglobin
Dwivedi and Flora (2011)	Oral	rat	leukocyte count
Dwivedi and Flora (2011)	Oral	rat	mean corpuscular hemoglobin
Dwivedi and Flora (2011)	Oral	rat	mean corpuscular hemoglobin concentration
Dwivedi and Flora (2011)	Oral	rat	mean corpuscular volume
Dwivedi and Flora (2011)	Oral	rat	platelet count and morphologic assessment
Flora et al. (2012)	Oral	mice	hematology, unspecified
Nain and Smits (2012)	Oral	rat	spleen: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	bone marrow: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Antonio Garcia et al. (2013)	Oral	rat	hematology, unspecified
Dávila-Esqueda et al. (2011)	Oral	rat	hematology, unspecified
Tokar et al. (2010b)	Oral	mice	leukemia (4 Types)
Tokar et al. (2010b)	Oral	mice	spleen: nonneoplastic lesions (2

			Types)
Tokar et al. (2012)	Oral	mice	vascular: neoplastic lesions (2 Types)
Waalkes et al. (2004b)	Oral	mice	spleen: nonneoplastic lesions (2 Types)
Waalkes et al. (2006a)	Oral	mice	spleen: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	spleen: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	spleen: neoplastic lesions (2 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	rat	hematology, unspecified
Blair et al. (1990b)	Inhalation	mice	hematology, unspecified
Blair et al. (1990b)	Inhalation	rat	spleen: absolute weight
Blair et al. (1990b)	Inhalation	rat	spleen: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	mice	spleen: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	mice	spleen: relative weight
Blair et al. (1990a)	Inhalation	mice	hematology, unspecified (2 Types)
Hong et al. (1989)	Inhalation	mice	bone marrow: nonneoplastic lesions (3 Types)
Hong et al. (1989)	Inhalation	mice	hematology, unspecified
Hong et al. (1989)	Inhalation	mice	hematopoietic system: nonneoplastic lesions
Hong et al. (1989)	Inhalation	mice	spleen: absolute weight
Hong et al. (1989)	Inhalation	mice	spleen: nonneoplastic lesions
Hong et al. (1989)	Inhalation	mice	spleen: relative weight
Ferzand et al. (2008)	Oral	mice	hematology, unspecified
Ferzand et al. (2008)	Oral	mice	spleen: nonneoplastic lesions
Odstrcil et al. (2010)	Oral	rat	hematology, unspecified
Sankar et al. (2013)	Oral	rat	spleen: relative weight
Yen et al. (2007)	Oral	mice	hematology, unspecified

3.2.9 Summary of Toxicology Studies for Hazard Identification for Immune System and Lymphatic Effects

Health Effect Category Route of Exposure Study Type	Count
Immune System and Lymphatic Effects	**24**
Oral	20
Chronic (>90 days)	6
Subchronic (30 days to < 90 days)	7
Reproductive/Developmental	7
Inhalation	4
Subchronic (30 days to < 90 days)	4

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Das et al. (2012b)	Oral	goat	cell-mediated immunity effects
Das et al. (2012b)	Oral	goat	immunoglobulin
Nain and Smits (2012)	Oral	rat	antibody (B cell) mediated immunity: general (2 Types)
Nain and Smits (2012)	Oral	rat	innate immunity/inflammation: general
Stępnik et al. (2009)	Oral	mice	immune and lymphatic system: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	lymphoma
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Ramsey et al. (2013b)	Oral	mice	innate immunity/inflammation: functional (2 Types)
Ramsey et al. (2013b)	Oral	mice	innate immunity/inflammation: general (2 Types)
Tokar et al. (2010b)	Oral	mice	lymphoma (2 Types)
Waalkes et al. (2006a)	Oral	mice	thymus: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	lymphoma
Waalkes et al. (2006b)	Oral	mice	thymus: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	thymus: neoplastic lesions (2 Types)

SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	rat	immune and lymphatic system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	mice	immune and lymphatic system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	thymus: absolute weight
Blair et al. (1990b)	Inhalation	mice	thymus: absolute weight
Kozul et al. (2009)	Oral	mice	innate immunity/inflammation: functional
Kozul et al. (2009)	Oral	mice	innate immunity/inflammation: general
Kozul et al. (2009)	Oral	mice	lymph node: function
Kozul et al. (2009)	Oral	mice	lymph node: gross pathology
Ramsey et al. (2013b)	Oral	mice	innate immunity/inflammation: functional (2 Types)
Sankar et al. (2013)	Oral	rat	antibody-mediated immunity effects (2 Types)
Sankar et al. (2013)	Oral	rat	immunoglobulin (2 Types)

3.2.10 Summary of Toxicology Studies for Hazard Identification for Liver Effects

Health Effect Category Route of Exposure Study Type	Count
Liver Effects	**36**
Oral	32
Chronic (>90 days)	11
Subchronic (30 days to < 90 days)	8
Reproductive/Developmental	13
Inhalation	4
Subchronic (30 days to < 90 days)	4

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Ghatak et al. (2011)	Oral	mice	liver: biochemistry
Ghatak et al. (2011)	Oral	mice	liver: nonneoplastic lesions (2 Types)
Arteel et al. (2008)	Oral	mice	liver: absolute weight
Arteel et al. (2008)	Oral	mice	liver: nonneoplastic lesions
Arteel et al. (2008)	Oral	mice	liver: relative weight
Flora et al. (2012)	Oral	mice	liver: nonneoplastic lesions
Liu et al. (2000)	Oral	mice	liver: nonneoplastic lesions (2 Types)
Liu et al. (2000)	Oral	mice	liver: relative weight (2 Types)
Nain and Smits (2012)	Oral	rat	liver: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	liver: neoplastic lesions
Stępnik et al. (2009)	Oral	mice	liver: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Reilly et al. (2013)	Oral	rat	liver: nonneoplastic lesions
Kozul-Horvath et al. (2012)	Oral	mice	liver: nonneoplastic lesions
Pineda et al. (2013)	Oral	rat	liver: absolute weight
Pineda et al. (2013)	Oral	rat	liver: relative weight
Ríos et al. (2012)	Oral	rat	liver: nonneoplastic lesions
Tokar et al. (2010b)	Oral	mice	liver: nonneoplastic lesions (2

			Types)
Tokar et al. (2011)	Oral	mice	liver: neoplastic lesions (6 Types)
Tokar et al. (2012)	Oral	mice	liver: neoplastic lesions (3 Types)
Waalkes et al. (2004b)	Oral	mice	liver: neoplastic lesions (8 Types)
Waalkes et al. (2006a)	Oral	mice	liver: neoplastic lesions (2 Types)
Waalkes et al. (2006a)	Oral	mice	liver: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	liver: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	liver: neoplastic lesions (8 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	liver: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	liver: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	mice	liver: relative weight
Blair et al. (1990b)	Inhalation	rat	liver: relative weight
Fouad et al. (2012)	Oral	mice	liver: nonneoplastic lesions
Owumi et al. (2013)	Oral	rat	liver: nonneoplastic lesions
Patra et al. (2012)	Oral	goat	liver: nonneoplastic lesions
Bashir et al. (2006)	Oral	rat	liver: absolute weight
Bashir et al. (2006)	Oral	rat	liver: nonneoplastic lesions
Ferzand et al. (2008)	Oral	mice	liver: nonneoplastic lesions
Kharroubi et al. (2014)	Oral	rat	liver: nonneoplastic lesions
Odstrcil et al. (2010)	Oral	rat	liver: gross pathology

3.2.11 Summary of Toxicology Studies for Hazard Identification for Mortality

Health Effect Category Route of Exposure Study Type	Count
Mortality	**1**
Oral	1
Reproductive/Developmental	1

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Miyazaki et al. (2005)	Oral	mice	mortality

3.2.12 Summary of Toxicology Studies for Hazard Identification for Nervous System Effects

Health Effect Category Route of Exposure Study Type	Count
Nervous System Effects	**35**
Oral	33
Chronic (>90 days)	8
Subchronic (30 days to < 90 days)	18
Reproductive/Developmental	7
Inhalation	2
Subchronic (30 days to < 90 days)	2

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
(Nagaraja and Desiraju, 1993, pp. author-year)	Oral	rat	brain: absolute weight
(Nagaraja and Desiraju, 1993, pp. author-year)	Oral	rat	brain: biochemical parameters (2 Types)
Bardullas et al. (2009)	Oral	mice	brain: neurotransmitter (14 Types)
Bardullas et al. (2009)	Oral	mice	locomotor activity (2 Types)
Dwivedi and Flora (2011)	Oral	rat	cholinesterase activity (2 Types)
Flora et al. (2012)	Oral	mice	brain: nonneoplastic lesions
Liu et al. (2012)	Oral	mice	brain: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	nervous system: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Chattopadhyay et al. (2002)	Oral	rat	brain: gross pathology
Chattopadhyay et al. (2002)	Oral	rat	motor activity
Herrera et al. (2013)	Oral	rat	cholinesterase activity
Martinez et al. (2008)	Oral	mice	brain: biochemical parameters
Ríos et al. (2012)	Oral	rat	brain: nonneoplastic lesions
Srivastava et al. (2007)	Oral	mice	vascular: function
Xi et al. (2009)	Oral	rat	CNS: function - cognition (3 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			

Study References	Route of Exposure	Species	Health Effect
Blair et al. (1990b)	Inhalation	mice	nervous system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	nervous system: nonneoplastic lesions
Nagaraja and Desiraju (1994)	Oral	rat	brain: absolute weight
Nagaraja and Desiraju (1994)	Oral	rat	brain: biochemical parameters
Nagaraja and Desiraju (1994)	Oral	rat	brain: function (other than FOB)
García-Chávez et al. (2007)	Oral	rat	CNS: neurochemical alterations and conduction
García-Chávez et al. (2007)	Oral	rat	nervous system: neoplastic lesions
Nagaraja and Desiraju (1994)	Oral	rat	brain: absolute weight
Nagaraja and Desiraju (1994)	Oral	rat	brain: biochemical parameters
Nagaraja and Desiraju (1994)	Oral	rat	brain: function (other than FOB)
Jing et al. (2012)	Oral	rat	brain: function (other than FOB) (2 Types)
Jing et al. (2012)	Oral	rat	brain: nonneoplastic lesions
Luo et al. (2009)	Oral	rat	brain: function (other than FOB)
Luo et al. (2009)	Oral	rat	brain: nonneoplastic lesions
Sharma and Sharma (2013)	Oral	rat	brain: biochemical parameters
Sharma and Sharma (2013)	Oral	rat	brain: function (other than FOB)
Sharma and Sharma (2013)	Oral	rat	functional observation battery/neuro-behavioral
Wang et al. (2009c)	Oral	mice	brain: function (other than FOB)
Zhang et al. (2013b)	Oral	mice	brain: gross pathology
Zhang et al. (2013b)	Oral	mice	brain: neurotransmitter (12 Types)

3.2.13 Summary of Toxicology Studies for Hazard Identification for Other

Health Effect Category Route of Exposure Study Type	Count
Other	**30**
Oral	30
Chronic (>90 days)	8
Subchronic (30 days to < 90 days)	11
Reproductive/Developmental	11

Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
(Nagaraja and Desiraju, 1993, pp. author-year)	Oral	rat	body weight
(Nagaraja and Desiraju, 1993, pp. author-year)	Oral	rat	food consumption
Liu et al. (2000)	Oral	mice	body weight (2 Types)
Nain and Smits (2012)	Oral	rat	body weight gain
Nain and Smits (2012)	Oral	rat	food consumption
Nain and Smits (2012)	Oral	rat	water consumption
Stępnik et al. (2009)	Oral	mice	bone: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	musculoskeletal system: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Shaw (1973)	Oral	rat	tooth: nonneoplastic lesions (3 Types)
Miyazaki et al. (2005)	Oral	mice	body weight gain
Mehranjani and Taefi (2012)	Oral	rat	body weight
Dávila-Esqueda et al. (2012)	Oral	rat	body weight
Dávila-Esqueda et al. (2011)	Oral	rat	body weight
Kozul-Horvath et al. (2012)	Oral	mice	body weight gain
Martinez et al. (2008)	Oral	mice	postnatal body weight
Martinez-Finley et al. (2009)	Oral	mice	body weight (2 Types)
Ramsey et al. (2013c)	Oral	mice	water consumption

Ramsey et al. (2013b)	Oral	mice	body weight (2 Types)
Waalkes et al. (2003)	Oral	mice	total body neoplastic lesions (4 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Nagaraja and Desiraju (1994)	Oral	rat	body weight
Shaw (1973)	Oral	rat	tooth: nonneoplastic lesions (2 Types)
Nagaraja and Desiraju (1993)	Oral	rat	body weight
Nagaraja and Desiraju (1993)	Oral	rat	food consumption
Nagaraja and Desiraju (1994)	Oral	rat	body weight
Jing et al. (2012)	Oral	rat	body weight
Kozul et al. (2009)	Oral	mice	body weight
Lemaire et al. (2011)	Oral	mice	body weight
Luo et al. (2009)	Oral	rat	body weight
Odstrcil et al. (2010)	Oral	rat	bone: gross pathology
Odstrcil et al. (2010)	Oral	rat	bone: nonneoplastic lesions (2 Types)

3.2.14 Summary of Toxicology Studies for Hazard Identification for Renal Effects

Health Effect Category Route of Exposure Study Type	Count
Renal Effects	**28**
Oral	24
Chronic (>90 days)	4
Subchronic (30 days to < 90 days)	4
Reproductive/Developmental	16
Inhalation	4
Subchronic (30 days to < 90 days)	4

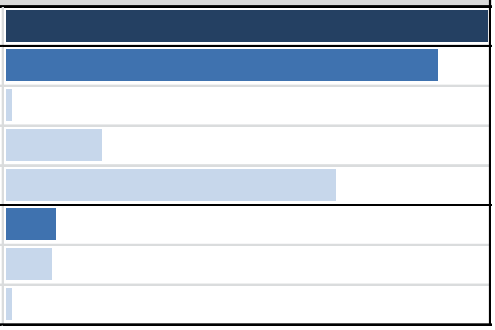
Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Liu et al. (2000)	Oral	mice	kidney: nonneoplastic lesions (2 Types)
Liu et al. (2000)	Oral	mice	kidney: relative weight (2 Types)
Nain and Smits (2012)	Oral	rat	kidney: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	kidney: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Rogers et al. (2014)	Oral	rat	kidney: function
Rogers et al. (2014)	Oral	rat	kidney: nonneoplastic lesions
Pineda et al. (2013)	Oral	rat	kidney: absolute weight
Pineda et al. (2013)	Oral	rat	kidney: relative weight
Tokar et al. (2010b)	Oral	mice	kidney: nonneoplastic lesions (2 Types)
Tokar et al. (2011)	Oral	mice	kidney: neoplastic lesions (5 Types)
Tokar et al. (2011)	Oral	mice	kidney: nonneoplastic lesions (2 Types)
Tokar et al. (2012)	Oral	mice	kidney: neoplastic lesions (3 Types)
Tokar et al. (2012)	Oral	mice	kidney: nonneoplastic lesions
Tokar et al. (2012)	Oral	mice	urinary bladder: neoplastic lesions
Waalkes et al. (2004b)	Oral	mice	kidney: nonneoplastic lesions (2 Types)

Waalkes et al. (2006a)	Oral	mice	kidney: neoplastic lesions
Waalkes et al. (2006a)	Oral	mice	kidney: nonneoplastic lesions (2 Types)
Waalkes et al. (2006b)	Oral	mice	kidney: neoplastic lesions
Waalkes et al. (2006b)	Oral	mice	kidney: nonneoplastic lesions
Waalkes et al. (2003)	Oral	mice	kidney: neoplastic lesions (2 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	kidney: absolute weight
Blair et al. (1990b)	Inhalation	mice	kidney: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	kidney: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	kidney: relative weight
Ferzand et al. (2008)	Oral	mice	kidney: nonneoplastic lesions
Majhi et al. (2011)	Oral	rat	kidney: absolute weight (2 Types)
Majhi et al. (2011)	Oral	rat	kidney: relative weight (2 Types)
Odstrcil et al. (2010)	Oral	rat	kidney: gross pathology

3.2.15 Summary of Toxicology Studies for Hazard Identification for Reproductive System Effects including Pregnancy Outcomes

Health Effect Category Route of Exposure Study Type	Count
Reproductive System Effects including Pr	**95**
Oral	85
Chronic (>90 days)	1
Subchronic (30 days to < 90 days)	19
Reproductive/Developmental	65
Inhalation	10
Subchronic (30 days to < 90 days)	9
Reproductive/Developmental	1



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Stępnik et al. (2009)	Oral	mice	female reproductive system: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Nagymajtenyi et al. (1985)	Inhalation	mice	number of live fetuses
Aggarwal et al. (2007)	Oral	rat	corpora lutea
Aggarwal et al. (2007)	Oral	rat	implantations
Aggarwal et al. (2007)	Oral	rat	number of dead fetuses
Aggarwal et al. (2007)	Oral	rat	number of live fetuses
Aggarwal et al. (2007)	Oral	rat	postimplantation loss
Aggarwal et al. (2007)	Oral	rat	preimplantation loss
Aggarwal et al. (2007)	Oral	rat	resorption: unspecified
Aggarwal et al. (2007)	Oral	rat	sex ratio
Aggarwal et al. (2007)	Oral	rat	uterus: absolute weight
Gandhi et al. (2012)	Oral	rat	gestation length
Gandhi et al. (2012)	Oral	rat	neonatal/infant mortality
Miyazaki et al. (2005)	Oral	mice	litter size
Reilly et al. (2013)	Oral	rat	mammary gland: nonneoplastic lesions
Mehranjani and Taefi (2012)	Oral	rat	testis: absolute weight

Mehranjani and Taefi (2012)	Oral	rat	testis: nonneoplastic lesions
Chattopadhyay et al. (2002)	Oral	rat	gestation index (%)
Cronican et al. (2013)	Oral	mice	litter size
Dávila-Esqueda et al. (2012)	Oral	rat	estrogen
Dávila-Esqueda et al. (2012)	Oral	rat	estrous cyclicity (3 Types)
Dávila-Esqueda et al. (2012)	Oral	rat	female reproductive system: nonneoplastic lesions
Dávila-Esqueda et al. (2012)	Oral	rat	ovary: absolute weight
Dávila-Esqueda et al. (2012)	Oral	rat	progesterone
Dávila-Esqueda et al. (2012)	Oral	rat	uterus: absolute weight
He et al. (2007)	Oral	mice	birth index (3 Types)
He et al. (2007)	Oral	mice	litter size (3 Types)
He et al. (2007)	Oral	mice	postimplantation loss (2 Types)
He et al. (2007)	Oral	mice	resorption: unspecified
Kozul-Horvath et al. (2012)	Oral	mice	live births
Markowski et al. (2012)	Oral	mice	body weight gain
Markowski et al. (2012)	Oral	mice	gestation length
Markowski et al. (2012)	Oral	mice	litter size
Martinez et al. (2008)	Oral	mice	litter size
Ramsey et al. (2013a)	Oral	mice	birth weight
Ramsey et al. (2013a)	Oral	mice	gestation length (3 Types)
Ramsey et al. (2013a)	Oral	mice	litter size (3 Types)
Ramsey et al. (2013c)	Oral	mice	gestation length
Ramsey et al. (2013c)	Oral	mice	litter size
Ramsey et al. (2013b)	Oral	mice	gestation length (2 Types)
Ramsey et al. (2013b)	Oral	mice	litter size (2 Types)
Tokar et al. (2010b)	Oral	mice	oviduct: nonneoplastic lesions
Tokar et al. (2010b)	Oral	mice	testis: nonneoplastic lesions
Tokar et al. (2010b)	Oral	mice	uterus: neoplastic lesions (6 Types)
Tokar et al. (2010b)	Oral	mice	uterus: nonneoplastic lesions
Tokar et al. (2011)	Oral	mice	ovary: neoplastic lesions (3 Types)
Tokar et al. (2011)	Oral	mice	oviduct: neoplastic lesions
Tokar et al. (2011)	Oral	mice	oviduct: nonneoplastic lesions
Tokar et al. (2011)	Oral	mice	uterus: neoplastic lesions (4 Types)
Tokar et al. (2011)	Oral	mice	uterus: nonneoplastic lesions
Waalkes et al. (2004b)	Oral	mice	ovary: neoplastic lesions
Waalkes et al. (2004b)	Oral	mice	oviduct: nonneoplastic lesions
Waalkes et al. (2004b)	Oral	mice	uterus: nonneoplastic lesions
Waalkes et al. (2006a)	Oral	mice	testis: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	cervix: neoplastic lesions
Waalkes et al. (2006b)	Oral	mice	ovary: neoplastic lesions
Waalkes et al. (2006b)	Oral	mice	ovary: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	oviduct: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	urogenital system: neoplastic

			lesions (6 Types)
Waalkes et al. (2006b)	Oral	mice	uterus: neoplastic lesions
Waalkes et al. (2006b)	Oral	mice	vulva: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	ovary: neoplastic lesions (3 Types)
Waalkes et al. (2003)	Oral	mice	oviduct: neoplastic lesions (2 Types)
Waalkes et al. (2003)	Oral	mice	oviduct: nonneoplastic lesions
Waalkes et al. (2003)	Oral	mice	testis: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	uterus: neoplastic lesions (2 Types)
Waalkes et al. (2003)	Oral	mice	uterus: nonneoplastic lesions
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Omura et al. (1996)	Inhalation	rat	epididymis: absolute weight
Omura et al. (1996)	Inhalation	rat	epididymis: relative weight
Omura et al. (1996)	Inhalation	rat	sperm parameters (4 Types)
Omura et al. (1996)	Inhalation	rat	testis: absolute weight
Omura et al. (1996)	Inhalation	rat	testis: relative weight
Blair et al. (1990b)	Inhalation	mice	female reproductive system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	female reproductive system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	male reproductive system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	mice	male reproductive system: nonneoplastic lesions
Momeni et al. (2012)	Oral	rat	sperm parameters (4 Types)
Momeni et al. (2012)	Oral	rat	testis: absolute weight
Momeni and Eskandari (2012)	Oral	rat	sperm parameters (6 Types)
Momeni and Eskandari (2012)	Oral	rat	testis: absolute weight
Owumi et al. (2013)	Oral	rat	sperm parameters
Ferreira et al. (2012)	Oral	mice	epididymis: absolute weight
Ferreira et al. (2012)	Oral	mice	epididymis: relative weight
Ferreira et al. (2012)	Oral	mice	sperm parameters
Ferreira et al. (2012)	Oral	mice	testis: absolute weight
Ferreira et al. (2012)	Oral	mice	testis: gross pathology
Ferreira et al. (2012)	Oral	mice	testis: relative weight
Pant et al. (2001)	Oral	mice	epididymis: absolute weight
Pant et al. (2001)	Oral	mice	epididymis: relative weight
Pant et al. (2001)	Oral	mice	male accessory sex gland: absolute weight (3 Types)
Pant et al. (2001)	Oral	mice	male accessory sex gland: relative weight (3 Types)
Pant et al. (2001)	Oral	mice	sperm parameters (3 Types)
Pant et al. (2001)	Oral	mice	steroidogenic enzyme activity (6

			Types)
Pant et al. (2001)	Oral	mice	testis: absolute weight
Pant et al. (2001)	Oral	mice	testis: relative weight

3.2.16 Summary of Toxicology Studies for Hazard Identification for Respiratory Effects

Health Effect Category Route of Exposure Study Type	Count
Respiratory Effects	**22**
Oral	20
Chronic (>90 days)	3
Subchronic (30 days to < 90 days)	2
Reproductive/Developmental	15
Inhalation	2
Subchronic (30 days to < 90 days)	2

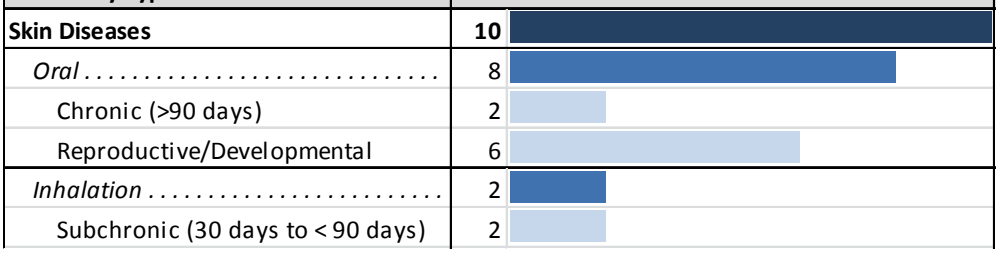
Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Singh et al. (2010)	Oral	mice	lung: nonneoplastic lesions
Nain and Smits (2012)	Oral	rat	lung: nonneoplastic lesions
Stępnik et al. (2009)	Oral	mice	respiratory system: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Lantz et al. (2009)	Oral	mice	lung: function (2 Types)
Ramsey et al. (2013a)	Oral	mice	lung: function (5 Types)
Ramsey et al. (2013a)	Oral	mice	lung: gross pathology (3 Types)
Ramsey et al. (2013c)	Oral	mice	lung: function (8 Types)
Ramsey et al. (2013c)	Oral	mice	lung: gross pathology (2 Types)
Ramsey et al. (2013b)	Oral	mice	innate immunity/inflammation: general (6 Types)
Tokar et al. (2010b)	Oral	mice	lung: neoplastic lesions (4 Types)

Tokar et al. (2010b)	Oral	mice	lung: nonneoplastic lesions (2 Types)
Tokar et al. (2011)	Oral	mice	lung: neoplastic lesions (6 Types)
Tokar et al. (2012)	Oral	mice	lung: neoplastic lesions (4 Types)
Waalkes et al. (2004b)	Oral	mice	lung: neoplastic lesions (2 Types)
Waalkes et al. (2006a)	Oral	mice	lung: neoplastic lesions (2 Types)
Waalkes et al. (2006a)	Oral	mice	lung: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	lung: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	lung: neoplastic lesions (4 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	respiratory system: nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	respiratory system: nonneoplastic lesions
Lantz et al. (2009)	Oral	mice	lung: function (2 Types)
Ramsey et al. (2013b)	Oral	mice	lung: function (2 Types)

3.2.17 Summary of Toxicology Studies for Hazard Identification for Skin Diseases

Health Effect Category Route of Exposure Study Type	Count
Skin Diseases	**10**
Oral	8
Chronic (>90 days)	2
Reproductive/Developmental	6
Inhalation	2
Subchronic (30 days to < 90 days)	2



Note: Studies may be placed in more than one category depending upon the data presented. Therefore, the totals may not sum to the total number of studies presented in the figure.

CHRONIC (>90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Germolec et al. (1998)	Oral	mice	skin and subcutaneous tissue: neoplastic lesions
Stępnik et al. (2009)	Oral	mice	skin and subcutaneous tissue: nonneoplastic lesions
REPRODUCTIVE/DEVELOPMENTAL			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Tokar et al. (2010b)	Oral	mice	skin and subcutaneous tissue: neoplastic lesions (2 Types)
Waalkes et al. (2004b)	Oral	mice	skin and subcutaneous tissue: nonneoplastic lesions (2 Types)
Waalkes et al. (2006a)	Oral	mice	skin and subcutaneous tissue: nonneoplastic lesions
Waalkes et al. (2006b)	Oral	mice	skin and subcutaneous tissue: neoplastic lesions
Waalkes et al. (2008)	Oral	mice	skin and subcutaneous tissue: neoplastic lesions
Waalkes et al. (2003)	Oral	mice	skin and subcutaneous tissue: neoplastic lesions (2 Types)
SUBCHRONIC (30 DAYS TO <90 DAYS)			
Study References	**Route of Exposure**	**Species**	**Health Effect**
Blair et al. (1990b)	Inhalation	mice	skin and subcutaneous tissue:

			nonneoplastic lesions
Blair et al. (1990b)	Inhalation	rat	skin and subcutaneous tissue: nonneoplastic lesions

4 SUMMARY OF RISK OF BIAS EVALUATIONS FOR INORGANIC ARSENIC EPIDEMIOLOGIC STUDIES

4.1 Risk of Bias Overview - Clinical Chemistry and Urinalysis

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Casale et al. (2013)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	-	-	+	+	+	++
Chen et al. (2011c)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	+	++	++	+	++
Das et al. (2012a)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	-	+	+	++
Islam et al. (2011)*	P	n/a	n/a	++	++	++	n/a	+	n/a	+	+	+	+	++	+	++
Kim et al. (2013)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	-	-	+	+	+	++
Maiti et al. (2012)*	P	n/a	n/a	++	+	-	n/a	+	n/a	++	-	-	-	+	+	+
Mazumder et al. (2013)*	P	n/a	n/a	++	++	++	n/a	+	n/a	-	-	-	++	+	+	++
Nabi et al. (2005)	S	n/a	n/a	-	-	+	n/a	+	n/a	-	-	-	-	-	+	-
Shen et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	-	-	-	++	+	+

*Data not yet included in accompanying evidence tables. Abbreviations: Att (attrition/exclusion); SRB (Selective Reporting Bias)

4.2 Risk of Bias Overview - Endocrine System Effects including Diabetes

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Chen et al. (2012a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	+	++	+	++
Chen et al. (2010c)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	++	+	++	++	+	+
Chen et al. (2011a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	++	++	+	++
Ciarrocca et al. (2012)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	++	++	+	+
Coronado-González et al. (2007)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	+	++	+	++
Del Razo et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	+	+	+	++
Drobná et al. (2013)*	P	n/a	n/a	+	++	+	n/a	+	n/a	++	-	-	-	+	+	+
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Ettinger et al. (2009)	P	n/a	n/a	+	++	-	n/a	+	n/a	+	++	-	++	++	+	++
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Gribble et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	++	++	++	+	++
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Hsieh et al. (2008a)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	+	+	+	+	++
Hsu et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Islam et al. (2012b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	++	+	-	+	+
James et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	+	+	++
Jensen and Hansen (1998)	P	n/a	n/a	-	+	-	n/a	+	n/a	-	+	-	+	+	+	++
Jovanovic et al. (2013)	S	n/a	n/a	-	--	+	n/a	+	n/a	+	+	-	--	+	++	++
Kim and Lee (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	++	+	+	+
Kim et al. (2013)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	-	-	+	+	+	++
Lai et al. (1994)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	-	-	-	+	+	+
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Li et al. (2013a)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	+	-	+	+	++
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Maiti et al. (2012)*	P	n/a	n/a	++	+	-	n/a	+	n/a	++	-	-	-	+	+	+
Makris et al. (2012)	S	n/a	n/a	++	+	+	n/a	+	n/a	+	-	+	--	-	+	+

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Navas-Acien et al. (2008)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	+	++	+	+	++
Navas-Acien et al. (2009)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	+	++	+	+	++
Nizam et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	-	+	+	++
Ojajarvi et al. (2000)	S	n/a	n/a	-	+	-	n/a	+	n/a	+	-	-	--	-	+	++
Pan et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	+	++	+	++
Rahman and Axelson (1995)	S	n/a	n/a	-	-	-	n/a	+	n/a	++	-	-	-	-	+	-
Rahman and Axelson (2001)	S	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	-	-	+	-
Rahman et al. (1996)	S	n/a	n/a	+	-	-	n/a	+	n/a	++	+	-	--	+	+	+
Rahman et al. (1998)	S	n/a	n/a	--	+	+	n/a	+	n/a	++	-	-	-	-	+	-
Rahman et al. (1999b)*	P	n/a	n/a	++	+	+	n/a	+	n/a	++	-	-	-	-	+	++
Rhee et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	-	++	++	+	++
Sawada et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	++	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Steinmaus et al. (2009)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Tseng et al. (2000)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	-	-	-	++	+	++
Zierold et al. (2004)*	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	+	-	-	+	+

*Data not yet included in accompanying evidence tables.

4.3 Risk of Bias Overview - Hematology, Hematopoietic System

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Del Razo et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	+	+	+	++
Ghosh (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	-	-	-	+	++
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Heck et al. (2008)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	++	-	+	++
Hopenhayn et al. (2006)	S	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	-	-	+	++
Maiti et al. (2012)*	P	n/a	n/a	++	+	-	n/a	+	n/a	++	-	-	-	+	+	+
Majumdar et al. (2009)	P	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	++
Saha et al. (2013)	P	n/a	n/a	+	+	+	n/a	+	n/a	+	++	-	-	+	+	++

*Data not yet included in accompanying evidence tables.

4.4 Risk of Bias Overview - Liver Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Baastrup et al. (2008)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	+	+	-
Chen et al. (1986)	S	n/a	n/a	++	+	-	n/a	+	n/a	+	+	+	--	++	+	++
Chung et al. (2012)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	-	++	+	+	++
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Ghosh (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	-	-	-	+	++
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Hsu et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Majumdar et al. (2009)	P	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	++
Paul et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	++	+	++
Sawada et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	++	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Tsuda et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	+
Wadhwa et al. (2011a)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	-	-	-

4.5 Risk of Bias Overview - Immune System and Lymphatic Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ahmed et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	++	+	+	+
Biswas et al. (2008)*	P	n/a	n/a	++	+	+	n/a	+	n/a	+	-	-	-	++	++	++
Bosnjak et al. (2008)	P	n/a	n/a	++	-	+	n/a	+	n/a	++	-	-	-	++	+	-
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Infante-Rivard et al. (2001)	S	n/a	n/a	++	+	--	n/a	+	n/a	++	+	-	-	++	+	++
Islam et al. (2007)	S	n/a	n/a	-	-	+	n/a	+	n/a	+	-	-	-	+	+	-
Josyula et al. (2006)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	+	+	+
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Lu and Chen (1991)	S	n/a	n/a	++	++	+	n/a	+	n/a	++	-	++	-	++	+	++
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Marsh et al. (2009)	S	n/a	n/a	+	+	++	n/a	+	n/a	++	+	+	-	+	+	+
Mazumder et al. (2000)	S	n/a	n/a	+	+	-	n/a	+	n/a	+	-	-	-	-	+	-
Milton and Rahman (2002)	S	n/a	n/a	-	-	-	n/a	+	n/a	-	-	-	-	-	-	-
Milton et al. (2001)	S	n/a	n/a	-	++	-	n/a	+	n/a	++	--	-	--	-	+	+
Moore et al. (2009)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	-	+	+	++	+	++
Pesola et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	+	+	++
Pinto et al. (1978)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Raqib et al. (2009)	P	n/a	n/a	++	-	+	n/a	+	n/a	+	+	+	++	-	+	++
Saha et al. (2013)	P	n/a	n/a	+	+	+	n/a	+	n/a	+	++	-	-	+	+	++
Shiue (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	+	+	+	+	++
Sohel et al. (2009)	P	n/a	n/a	++	+	+	n/a	+	n/a	+	-	+	+	+	+	++
Von Ehrenstein et al. (2005)	S	n/a	n/a	++	++	++	n/a	+	n/a	++	-	+	--	-	+	++
Wu et al. (2012b)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	-	-	++	++	+	++

* Data not yet included in accompanying evidence tables.

4.6 Risk of Bias Overview - Renal Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Baastrup et al. (2008)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	+	+	-
Boffetta et al. (2011)	S	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	--	++	+	++
Chen et al. (2011a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	++	++	+	++
Chiou et al. (2005)	P	n/a	n/a	+	-	+	n/a	+	n/a	++	++	++	+	++	+	++
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Enterline et al. (1995)	S	n/a	n/a	+	-	-	n/a	+	n/a	++	+	-	-	+	+	+
Eom et al. (2011)*	P	n/a	n/a	+	++	+	n/a	+	n/a	-	-	-	+	+	+	++
Feng et al. (2013)*	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	-	++	+	+	++
Ferreccio et al. (2013a)	P	n/a	n/a	++	++	++	n/a	+	n/a	+	+	-	-	++	-	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++
García-Vargas et al. (1994)*	P	n/a	n/a	+	+	++	n/a	+	n/a	++	-	-	-	+	+	+
Hawkesworth et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	++	+	++	+	++
Hernández-Zavala et al. (1999)*	P	n/a	n/a	-	+	++	n/a	+	n/a	+	-	-	+	++	+	++
Hsu et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Huang et al. (2011)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	-	++	++	+	+
Huang et al. (2012)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	+	-	++	++	+	++
Jayatilake et al. (2013)	S	n/a	n/a	-	++	-	n/a	+	n/a	++	-	-	-	-	+	++
Kurttio et al. (1999)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	-	++	+	+
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Mostafa and Cherry (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	+	-	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ng et al. (2005)	S	n/a	n/a	-	+	-	n/a	+	n/a	+	-	-	-	+	+	+
Palaneeswari et al. (2013)	S	n/a	n/a	-	--	+	n/a	+	n/a	++	+	-	-	-	+	-
Pi et al. (2005)*	P	n/a	n/a	++	+	+	n/a	+	n/a	-	-	-	++	+	+	+
Sawada et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	++	-	++	+	++
Yuan et al. (2010)	P	n/a	n/a	++	+	+	n/a	+	n/a	+	++	-	-	+	+	++

*Data not yet included in accompanying evidence tables.

4.7 Risk of Bias Overview - Mortality

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Pinto et al. (1978)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Rahman et al. (2013)	P	n/a	n/a	+	+	+	n/a	+	n/a	-	++	+	-	++	+	++
Sohel et al. (2009)	P	n/a	n/a	++	+	+	n/a	+	n/a	+	-	+	+	+	+	++
Tsuda et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	+
Wade et al. (2009)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	++	-	+	-	+	++
Welch et al. (1982)	S	n/a	n/a	-	+	+	n/a	+	n/a	+	+	-	-	++	+	+

4.8 Risk of Bias Overview - Digestive System Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Amaral et al. (2012)	P	n/a	n/a	+	++	++	n/a	+	n/a	-	+	-	+	+	+	++
Baastrup et al. (2008)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	+	+	-
Bulbulyan et al. (1996)	S	n/a	n/a	+	-	+	n/a	+	n/a	++	-	+	--	-	+	++
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Farzan et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	+	-	+	++
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Hsu et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Kreuzer et al. (2012)	S	n/a	n/a	+	+	-	n/a	+	n/a	+	-	-	-	-	+	++
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Pinto et al. (1977)	S	n/a	n/a	-	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Pinto et al. (1978)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	++	+	-

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Rahman et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	++	+	+	++
Sawada et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	++	-	++	+	++
Syed et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	++	++	++	+	++
Tsuda et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	+

4.9 Risk of Bias Overview - Cardiovascular Disease

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ahmad et al. (2006)*	P	n/a	n/a	++	++	-	n/a	+	n/a	++	++	+	-	+	+	++
Axelson et al. (1978)	S	n/a	n/a	+	-	+	n/a	+	n/a	++	++	++	-	++	+	+
Bosnjak et al. (2008)	P	n/a	n/a	++	-	+	n/a	+	n/a	++	-	-	-	++	+	-
Burgess et al. (2013)	P	n/a	n/a	+	++	-	n/a	+	n/a	+	-	-	++	++	+	+
Chen et al. (2012b)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	+	+	+	+	++	++
Chen et al. (2013a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	++	++	+	++
Chen et al. (1988)	S	n/a	n/a	++	++	--	n/a	+	n/a	++	+	+	--	+	+	++
Chen et al. (1995)	S	n/a	n/a	+	++	++	n/a	+	n/a	+	-	-	-	+	+	+
Chen et al. (1996)	P	n/a	n/a	+	++	++	n/a	+	n/a	++	+	+	-	++	+	+
Chen et al. (2006b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	+	+	+	-
Chen et al. (2007b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	+	++	+	++
Chen et al. (2011b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	+	++	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Chen et al. (2013c)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	++	++	+	++
Chiou et al. (1997)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	-	+	+	+	++
Chiou et al. (2001b)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	+	+	+	++
Chiou et al. (2005)	P	n/a	n/a	+	-	+	n/a	+	n/a	++	++	++	+	++	+	++
Cuzick et al. (1992)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	+	+	+
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Ghosh (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	-	-	-	+	++
Gong and O'Bryant (2012)	S	n/a	n/a	+	++	+	n/a	+	n/a	+	-	-	-	+	+	++
Guha Mazumder et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	+	++	+	+
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Hawkesworth et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	++	+	++	+	++
Hertz-Picciotto et al. (2000)	S	n/a	n/a	+	+	-	n/a	+	n/a	+	+	+	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Hsieh et al. (2008b)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	+	+	+	+
Hsieh et al. (2008a)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	+	+	+	+	++
Hsueh et al. (1998)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	+	+	+
Huang et al. (2007)*	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	++	+	+	+
Huang et al. (2009b)*	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	-	+	+	+	++
Islam et al. (2012a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	++	+	+	+	++
Jarup et al. (1989)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	+	+	++
Jensen and Hansen (1998)	P	n/a	n/a	-	+	-	n/a	+	n/a	-	+	-	+	+	+	++
Jones et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Karim et al. (2013)*	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	+	-	++	+	++
Kim and Lee (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	++	+	+	+
Kim et al. (2013)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	-	-	+	+	+	++
Kunrath et al. (2013)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	+	+	+	+	+	++
Kwok et al. (2007)	P	n/a	n/a	++	-	+	n/a	+	n/a	++	+	-	-	+	+	+

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Lagerkvist et al. (1986)	S	n/a	n/a	-	++	-	n/a	+	n/a	++	-	-	-	++	+	-
Lagerkvist et al. (1988)	S	n/a	n/a	++	+	-	n/a	+	n/a	+	-	+	-	+	+	+
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Li et al. (2013a)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	+	-	+	+	++
Li et al. (2009)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	-	-	+	+	++
Li et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	+	+	+	++
Liao et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	-	+	+	++
Liao et al. (2009)*	P	n/a	n/a	+	++	+	n/a	+	n/a	-	++	-	-	+	+	++
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Marsh et al. (2009)	S	n/a	n/a	+	+	++	n/a	+	n/a	++	+	+	-	+	+	+
Moon et al. (2013)	P	n/a	n/a	-	++	+	n/a	+	n/a	++	-	+	++	++	+	++
Mordukhovich et al. (2009)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	++	++	+	+
Mumford et al. (2007)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	++	-	++	++	+	++
Osorio-Yáñez et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	+	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Pi et al. (2005)*	P	n/a	n/a	++	+	+	n/a	+	n/a	-	-	-	++	+	+	+
Pinto et al. (1977)	S	n/a	n/a	-	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Pinto et al. (1978)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Rahman and Axelson (2001)	S	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	-	-	+	-
Rahman et al. (1999a)	P	n/a	n/a	++	-	+	n/a	+	n/a	++	-	-	-	++	+	+
Sohel et al. (2009)	P	n/a	n/a	++	+	+	n/a	+	n/a	+	-	+	+	+	+	++
Tseng et al. (1996)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	++	-	-	+	+	-
Tseng et al. (1997)	P	n/a	n/a	+	++	-	n/a	+	n/a	++	++	-	-	++	+	+
Tseng et al. (2003)	P	n/a	n/a	++	++	-	n/a	+	n/a	+	++	+	-	+	+	++
Wade et al. (2009)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	++	-	+	-	+	++
Wang et al. (2002)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	-	-	-	+	+	+
Wang et al. (2007c)*	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	-	++	+	+	+
Wang et al. (2009a)*	P	n/a	n/a	+	++	+	n/a	+	n/a	++	++	-	-	++	+	++
Wang et al. (2010)*	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Wang et al. (2011a)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	-	-	+	+	+	++
Welch et al. (1982)	S	n/a	n/a	-	+	+	n/a	+	n/a	+	+	-	-	++	+	+
Wu et al. (2006)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	+	+	+	++
Wu et al. (2010)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	+	+	+	+	++
Xia et al. (2009)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	++	-	+	+	+	++
Yildiz et al. (2008)	S	n/a	n/a	++	++	-	n/a	+	n/a	++	++	-	-	-	+	+
Zhang et al. (2013a)	S	n/a	n/a	+	+	--	n/a	+	n/a	+	++	-	--	++	+	++

* Data not yet included in accompanying evidence tables.

4.10Risk of Bias Overview - Other

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Akbal et al. (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	+	+	-
Bulbulyan et al. (1996)	S	n/a	n/a	+	-	+	n/a	+	n/a	++	-	+	--	-	+	++
Chiou et al. (1995)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	-	-	+	+	++
Chung et al. (2012)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	-	++	+	+	++
Cordova et al. (2013)*	P	n/a	n/a	-	-	+	n/a	+	n/a	++	+	-	+	++	+	+
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Enterline et al. (1995)	S	n/a	n/a	+	-	-	n/a	+	n/a	++	+	-	-	+	+	+
Fujino et al. (2004)*	P	n/a	n/a	++	++	-	n/a	+	n/a	++	-	+	-	+	+	-
Hsu et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Kurttio et al. (1998)*	P	n/a	n/a	+	++	+	n/a	+	n/a	-	--	-	-	-	-	-
Majumdar et al. (2009)	P	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	++
Mazumder et al. (2013)*	P	n/a	n/a	++	++	++	n/a	+	n/a	-	-	-	++	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Mitra et al. (2002)	P	n/a	n/a	+	-	+	n/a	+	n/a	++	-	+	-	-	+	++
Nakadaira et al. (2002)	S	n/a	n/a	+	+	-	n/a	+	n/a	+	+	-	--	-	+	-
Paul et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	++	+	++
Pinto et al. (1978)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Sińczuk-Walczak et al. (2010)	S	n/a	n/a	-	+	-	n/a	+	n/a	++	-	-	-	+	+	+
Sobel et al. (1987)	S	n/a	n/a	+	+	-	n/a	+	n/a	+	-	-	-	+	+	+
Syed et al. (2012)	S	n/a	n/a	++	+	+	n/a	+	n/a	++	-	++	--	++	+	++
Tsuda et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	+
Wang et al. (2011a)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	-	-	+	+	+	++

* Data not yet included in accompanying evidence tables.

4.11 Risk of Bias Overview - Reproductive System Effects including Pregnancy Outcomes

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ahmad et al. (2001)	S	n/a	n/a	++	++	+	n/a	+	n/a	+	-	++	-	-	+	++
Baastrup et al. (2008)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	+	+	-
Chakraborti et al. (2003)	S	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	-
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Garland et al. (1996)	P	n/a	n/a	+	++	++	n/a	+	n/a	-	+	+	-	++	+	++
Ihrig et al. (1998)	S	n/a	n/a	++	++	-	n/a	+	n/a	++	+	+	-	+	+	++
Kwok et al. (2006)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	+	+	++
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Milton et al. (2005)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	++	-	-	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Mukherjee et al. (2005)	S	n/a	n/a	-	-	+	n/a	+	n/a	+	-	-	-	-	+	-
Pollack et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	+	+	++	+	++
Rahman et al. (2010)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	+	+	+	+	+	++
Sawada et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	++	-	++	+	++
Sen and Chaudhuri (2008)	S	n/a	n/a	+	+	+	n/a	+	n/a	+	-	-	-	-	+	-
Sengupta et al. (2013)	P	n/a	n/a	+	++	-	n/a	+	n/a	+	-	-	+	++	+	++
Shen et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	-	-	-	++	+	+
Tsuda et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	+
Von Ehrenstein et al. (2006)	P	n/a	n/a	++	++	++	n/a	+	n/a	+	++	+	-	-	+	++
Xu et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	++	+	+	+

4.12Risk of Bias Overview - Skin Diseases

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ahmad et al. (1999)	S	n/a	n/a	-	-	+	n/a	+	n/a	+	-	-	-	-	+	+
Ahsan et al. (2000)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	-	-	+	+	+	-
Ahsan et al. (2006)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	-	++	+	+	++
Applebaum et al. (2007)*	P	n/a	n/a	+	+	+	n/a	+	n/a	++	+	+	++	++	+	++
Argos et al. (2007)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	+	+	+	+	++
Argos et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	++	+	+	++
Baastrup et al. (2008)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	+	+	-
Barati et al. (2010)	P	n/a	n/a	+	+	++	n/a	+	n/a	+	-	-	-	+	+	++
Beane Freeman et al. (2004)*	P	n/a	n/a	++	-	-	n/a	+	n/a	-	+	+	-	+	+	+
Bhowmick et al. (2013)	P	n/a	n/a	+	++	-	n/a	+	n/a	+	+	-	+	+	+	++
Borgono et al. (1977)	S	n/a	n/a	-	+	+	n/a	+	n/a	-	-	-	-	-	+	-
Breton et al. (2006)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	-	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Chakraborti et al. (2013b)	S	n/a	n/a	-	-	-	n/a	+	n/a	++	-	-	-	-	-	-
Chakraborti et al. (2003)	S	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	-
Chen et al. (2003a)*	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	++	+	++
Chen et al. (2006a)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	-	+	+	++
Chen et al. (2007c)*	P	n/a	n/a	-	++	+	n/a	+	n/a	++	++	+	+	+	+	++
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Fatmi et al. (2009)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	-	-	-	+	+	++
Fatmi et al. (2013)	P	n/a	n/a	+	-	-	n/a	+	n/a	+	-	-	+	+	+	-
Ghosh et al. (2007b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	++	-	+	+	++
Ghosh (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	-	-	-	+	++
Gilbert-Diamond et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	++	+	+	++
Guo et al. (2006b)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	++	-	-	++	+	++
Guo et al. (2006a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	-	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Hall et al. (2006)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	++	-	+	+	+	++
Haque et al. (2003)	S	n/a	n/a	++	++	++	n/a	-	n/a	++	-	+	-	--	+	++
Hashim et al. (2013)	P	n/a	n/a	++	-	-	n/a	+	n/a	-	-	-	++	-	+	+
Hon et al. (2012)*	P	n/a	n/a	++	-	++	n/a	+	n/a	-	+	+	-	++	+	++
Hsu et al. (2013a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Hsueh et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	-	+	-	-	++	+	+
Hsueh et al. (1997)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Karagas et al. (2001)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	+	++	+	+
Knobeloch et al. (2006)	P	n/a	n/a	++	+	+	n/a	+	n/a	++	+	+	++	+	+	++
Lamm et al. (2007)*	P	n/a	n/a	+	-	-	n/a	+	n/a	++	-	-	-	++	+	+
Leonardi et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	+	-	++	+	++
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Li et al. (2013a)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	+	-	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Lindberg et al. (2008)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	+	+	++
Lindberg et al. (2010)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	+	+	++	+	++
Liu et al. (2013)	S	n/a	n/a	+	--	-	n/a	+	n/a	++	-	-	-	+	+	++
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Maden et al. (2011)	P	n/a	n/a	+	-	-	n/a	+	n/a	+	--	-	++	+	+	++
Maharjan et al. (2005)	S	n/a	n/a	-	-	+	n/a	+	n/a	++	++	-	-	+	+	-
Maharjan et al. (2007)*	P	n/a	n/a	+	-	-	n/a	+	n/a	++	++	-	+	+	+	++
Mazumder et al. (1998)	P	n/a	n/a	-	+	+	n/a	+	n/a	+	+	-	-	-	+	++
Mazumder et al. (2013)*	P	n/a	n/a	++	++	++	n/a	+	n/a	-	-	-	++	+	+	++
McCarty et al. (2006)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	-	+	+	++
McDonald et al. (2007)	P	n/a	n/a	+	+	+	n/a	+	n/a	++	-	-	-	-	+	++
Melkonian et al. (2011)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	++	-	++	+	+	++
Mitra et al. (2002)	P	n/a	n/a	+	-	+	n/a	+	n/a	++	-	+	-	-	+	++
Mosaferi et al. (2008)	P	n/a	n/a	++	-	++	n/a	+	n/a	+	-	-	-	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Paul et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	++	+	++
Pavittranon et al. (2003)	S	n/a	n/a	-	-	-	n/a	+	n/a	-	-	-	-	-	+	-
Pei et al. (2013)	P	n/a	n/a	-	++	+	n/a	+	n/a	-	-	+	+	+	+	-
Perry et al. (1948)	S	n/a	n/a	-	-	--	n/a	+	n/a	++	-	-	-	-	+	-
Pesch et al. (2002)	S	n/a	n/a	++	++	++	n/a	+	n/a	+	+	-	-	++	+	++
Pesola et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	+	+	++
Pierce et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	+	++	+	++
Rahman et al. (2006a)	P	n/a	n/a	++	-	+	n/a	+	n/a	++	++	+	-	++	+	++
Ranft et al. (2003)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	-	-	+	++	+	++
Rosales-Castillo et al. (2004)*	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	-	+	+	+
Schäfer et al. (1999)*	P	n/a	n/a	-	-	++	n/a	+	n/a	-	-	-	-	+	+	+
Seow et al. (2012)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	-	++	+	+	++
Smith et al. (2000)	S	n/a	n/a	-	-	+	n/a	+	n/a	+	++	-	--	++	+	-
Surdu et al. (2013)	S	n/a	n/a	++	++	--	n/a	+	n/a	++	+	++	-	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Tondel et al. (1999)*	P	n/a	n/a	-	+	+	n/a	+	n/a	++	-	-	-	-	+	++
Valentine et al. (1991)	S	n/a	n/a	-	-	+	n/a	+	n/a	-	-	-	-	-	+	-
Valenzuela et al. (2005)	P	n/a	n/a	++	++	-	n/a	+	n/a	++	++	-	+	+	+	+
Xia et al. (2009)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	++	-	+	+	+	++

* Data not yet included in accompanying evidence tables.

4.13Risk of Bias Overview - Respiratory Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ades and Kazantzis (1988)	S	n/a	n/a	+	-	++	n/a	+	n/a	+	-	-	--	-	+	-
Axelson et al. (1978)	S	n/a	n/a	+	-	+	n/a	+	n/a	++	++	++	-	++	+	+
Baastrup et al. (2008)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	-	+	+	-
Begum et al. (2012)	S	n/a	n/a	-	-	+	n/a	+	n/a	-	-	-	-	-	+	++
Bulbulyan et al. (1996)	S	n/a	n/a	+	-	+	n/a	+	n/a	++	-	+	--	-	+	++
Chakraborti et al. (2013b)	S	n/a	n/a	-	-	-	n/a	+	n/a	++	-	-	-	-	-	-
Chattopadhyay et al. (2010)	S	n/a	n/a	-	-	-	n/a	+	n/a	++	-	+	-	-	+	-
Chen et al. (1986)	S	n/a	n/a	++	+	-	n/a	+	n/a	+	+	+	--	++	+	++
Chen et al. (2004a)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	-	++	+	++
Chen et al. (2010a)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	-	++	++	+	++
Chiou et al. (1995)	P	n/a	n/a	+	++	+	n/a	+	n/a	+	-	-	-	+	+	++
Chung et al. (2012)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	-	++	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
D'Errico et al. (2009)	S	n/a	n/a	++	++	++	n/a	+	n/a	++	+	-	-	++	+	++
Dauphiné et al. (2011)	P	n/a	n/a	+	++	++	n/a	+	n/a	++	-	+	-	-	+	+
Dauphiné et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	++	-	+	++	+	++
De et al. (2004)	S	n/a	n/a	+	+	+	n/a	+	n/a	-	-	-	-	-	-	-
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Enterline et al. (1987)	S	n/a	n/a	-	+	-	n/a	+	n/a	+	+	+	-	+	+	-
Enterline et al. (1995)	S	n/a	n/a	+	-	-	n/a	+	n/a	++	+	-	-	+	+	+
Farzan et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	+	-	+	++
Ferreccio et al. (1998)*	P	n/a	n/a	+	++	++	n/a	+	n/a	+	+	+	-	++	+	++
Ferreccio et al. (2000)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	+	-	++	+	++
Ferreccio et al. (2013b)	P	n/a	n/a	++	++	++	n/a	+	n/a	+	+	-	-	++	+	++
García-Esquinas et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	+	++	+	+	++
Ghosh et al. (2007b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	++	-	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Ghosh (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	-	-	-	+	++
Grimsrud et al. (2005)	S	n/a	n/a	+	++	++	n/a	+	n/a	++	-	+	-	-	+	-
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Halatek et al. (2009)	S	n/a	n/a	++	-	-	n/a	+	n/a	++	-	-	+	+	+	-
Heck et al. (2009)	P	n/a	n/a	++	++	++	n/a	+	n/a	+	+	+	++	++	+	++
Hsu et al. (2013b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Hsu et al. (2013a)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	++
Hu et al. (1999)	S	n/a	n/a	+	++	++	n/a	+	n/a	+	+	-	-	++	+	+
Jarup et al. (1989)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	+	+	++
Khlifi et al. (2014)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	-	+	++	+	++
Lee-Feldstein (1989)	S	n/a	n/a	+	-	-	n/a	+	n/a	++	-	-	-	-	++	++
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Lubin et al. (1981)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	+	-	-	+	+
Lubin et al. (2000)	S	n/a	n/a	+	+	+	n/a	+	n/a	+	-	-	-	-	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Lubin et al. (2008)	S	n/a	n/a	+	+	-	n/a	+	n/a	-	-	-	-	-	+	++
Majumdar et al. (2009)	P	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	++
Mazumder et al. (2005)	S	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	--	+	-	+
Milton et al. (2001)	S	n/a	n/a	-	++	-	n/a	+	n/a	++	--	-	--	-	+	+
Mostafa et al. (2008)*	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	-	-	++	+	+
Nafees et al. (2011)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	-	++	-	+	+	+
Nakadaira et al. (2002)	S	n/a	n/a	+	+	-	n/a	+	n/a	+	+	-	--	-	+	-
Parvez et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	+	++	++	+	++
Parvez et al. (2008)*	P	n/a	n/a	++	++	+	n/a	+	n/a	+	-	-	+	+	++	++
Parvez et al. (2010)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	++	-	++	-	+	++
Paul et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	++	+	++
Pinto et al. (1977)	S	n/a	n/a	-	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Pinto et al. (1978)	S	n/a	n/a	+	-	--	n/a	+	n/a	++	+	-	-	++	+	-
Rahman et al. (2011)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	+	+	++	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Raqib et al. (2009)	P	n/a	n/a	++	-	+	n/a	+	n/a	+	+	+	++	-	+	++
Sawada et al. (2013)	P	n/a	n/a	+	++	+	n/a	+	n/a	++	+	++	-	++	+	++
Smith et al. (2011)	S	n/a	n/a	++	++	+	n/a	+	n/a	+	++	-	-	+	+	+
Smith et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	+	-	-	-	++	+	++
Sorahan (2009)	S	n/a	n/a	-	-	-	n/a	+	n/a	-	-	-	--	-	+	++
Steinmaus et al. (2013)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	+	+	-	++	+	++
'T Mannetje et al. (2011)	S	n/a	n/a	++	++	++	n/a	+	n/a	++	+	-	-	-	+	++
Taylor et al. (1989)	S	n/a	n/a	+	++	--	n/a	+	n/a	++	+	+	-	++	+	++
Tsuda et al. (1995)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	-	++	+	+
Wadhwa et al. (2011b)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	-
Welch et al. (1982)	S	n/a	n/a	-	+	+	n/a	+	n/a	+	+	-	-	++	+	+

* Data not yet included in accompanying evidence tables.

4.14Risk of Bias Overview - Nervous System Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Adams et al. (2013)	P	n/a	n/a	+	-	+	n/a	+	n/a	++	++	+	+	+	+	++
Ali et al. (2010)	P	n/a	n/a	++	++	++	n/a	+	n/a	+	-	-	++	++	+	++
Blom et al. (1985)	S	n/a	n/a	+	++	-	n/a	+	n/a	++	-	-	-	+	+	++
Chakraborti et al. (2003)	S	n/a	n/a	-	-	+	n/a	+	n/a	++	-	-	-	-	+	-
Chiou et al. (2005)	P	n/a	n/a	+	-	+	n/a	+	n/a	++	++	++	+	++	+	++
Enterline and Marsh (1982)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	+	-	-	++	+	++
Feldman et al. (1979)	S	n/a	n/a	-	+	-	n/a	+	n/a	+	++	-	-	+	+	+
Ghosh et al. (2007b)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	++	-	+	+	++
Ghosh (2013)	S	n/a	n/a	-	-	-	n/a	+	n/a	+	-	-	-	-	+	++
Gong et al. (2011)	S	n/a	n/a	+	-	+	n/a	+	n/a	++	-	-	-	++	+	+
Guo et al. (2007)	S	n/a	n/a	-	--	-	n/a	+	n/a	-	-	-	-	-	+	-
Hafeman et al. (2005)	P	n/a	n/a	++	+	++	n/a	+	n/a	+	-	+	++	++	+	+

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Halatek et al. (2009)	S	n/a	n/a	++	-	-	n/a	+	n/a	++	-	-	+	+	+	-
Kreiss et al. (1983)	P	n/a	n/a	+	-	-	n/a	+	n/a	++	++	-	-	++	+	+
Lagerkvist and Zetterlund (1994)	S	n/a	n/a	+	++	+	n/a	+	n/a	++	-	-	-	++	+	+
Lewis et al. (1999)	P	n/a	n/a	+	-	+	n/a	+	n/a	+	+	-	-	++	+	-
Li et al. (2006)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	++	-	-	-	+	++
Lilis et al. (1985)*	P	n/a	n/a	++	+	+	n/a	+	n/a	+	++	-	-	-	+	++
Lin et al. (2008)	P	n/a	n/a	++	+	+	n/a	+	n/a	+	++	-	-	++	+	++
Mackenzie and Kyle (1984)	S	n/a	n/a	-	-	-	n/a	+	n/a	-	-	-	-	-	+	+
Mao et al. (2010)	S	n/a	n/a	+	+	+	n/a	+	n/a	++	++	-	-	-	+	-
O'Bryant et al. (2011)	S	n/a	n/a	++	++	-	n/a	+	n/a	-	+	-	-	++	+	++
Otto et al. (2006)	P	n/a	n/a	+	++	++	n/a	+	n/a	++	-	-	-	++	+	++
Otto et al. (2007)	P	n/a	n/a	+	++	++	n/a	+	n/a	+	++	-	++	++	+	++
Park et al. (2014)	P	n/a	n/a	+	+	++	n/a	+	n/a	++	+	-	-	+	+	+
Paul et al. (2013)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	+	-	+	++	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Rosado et al. (2007)	P	n/a	n/a	++	++	++	n/a	+	n/a	++	-	+	+	++	+	++
See et al. (2007)	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	-	-	++	+	++
Sińczuk-Walczak et al. (2010)	S	n/a	n/a	-	+	-	n/a	+	n/a	++	-	-	-	+	+	+
Tseng et al. (2006)	P	n/a	n/a	++	++	+	n/a	+	n/a	++	-	-	+	+	+	++
Zierold et al. (2004)*	P	n/a	n/a	++	++	+	n/a	+	n/a	+	++	+	-	-	+	+

* Data not yet included in accompanying evidence tables.

4.15References for Risk of Bias Evaluations for Epidemiologic Studies

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5 EVIDENCE TABLES FOR INORGANIC ARSENIC EPIDEMIOLOGIC STUDIES

Epidemiologic studies were limited to inorganic exposure where possible. However, measurements of asenic in urine may include inorganic arsenic, as well as arsenic metabolites. In general, biomarkers of exposure for arsenic represent total arsenic, and arsenic in drinking water represents inorganic arsenic.

5.1 Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults) n exposed: 56,378 n total: 57,053	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** not available	**Outcome: bladder cancer** ***cumulative arsenic exposure, mg*** Exp. Level: continuous; n: NR; IRR: 1; (CI): 0.98, 1.04 Stat Method: Cox regression
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-	**Outcome: bladder cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level: continuous; n: NR; IRR: 1.01; (CI): 0.93, 1.11 Stat Method: Cox regression

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	2004) **Population-Level Exposure:** 0.7 µg/L median	
Bates et al. (1995) **Study Type:** case-control **Location:** United States (Utah) **Population:** National Bladder Cancer Survey Utah adult respondents likely exposed to higher than average arsenic in drinking water n cases: 117 n control: 266	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic dose estimated from historical arsenic levels in public drinking water collected 1978-1979 combined with lifetime residential history and drinking water source at each residence **Population-Level Exposure:** 19-53 mg range	**Outcome: bladder cancer** ***cumulative arsenic dose - all subjects (quartiles), mg*** Exp. Level / n / adjOR / (CI) <19 / NR / 1 / n/a 19-<33 / NR / 1.56 / 0.8, 3.2 33-<53 / NR / 0.95 / 0.4, 2.0 ≥ 53 / NR / 1.41 / 0.7, 2.9 Stat Method: Unconditional multiple logistic regression analysis ***cumulative arsenic dose - ever smokers (quartiles), mg*** Exp. Level / n / adjOR / (CI) <19 / NR / 1 / n/a 19-<33 / NR / 3.33 / 1.0, 10.8 33-<53 / NR / 1.93 / 0.6, 6.2 ≥ 53 / NR / 3.32 / 1.1, 10.3 Stat Method: Unconditional multiple logistic regression analysis
	Exposure Surrogate: urine **Exposure Description:** estimated arsenic concentration in urine based on historic arsenic levels in public drinking water collected 1978-1979 combined with lifetime residential history, drinking water source at each residence, and ratio of water to total liquid intake **Population-Level Exposure:** 8-74 (mg/L) x yr. range	**Outcome: bladder cancer** ***urine arsenic concentration (30-39 years exposure) (quartiles), (mg/L) x yr.*** Exp. Level / n / adjOR / (CI) <8 / NR / 1 / n/a 8-<10 / NR / 1.27 / 0.4, 3.6 10-<13 / NR / 1.26 / 0.4, 3.6 ≥ 13 / NR / 3.07 / 1.1, 8.4 Stat Method: Unconditional multiple logistic regression analysis ***urine arsenic concentration (10-19 years exposure) (quartiles), (mg/L) x yr.*** Exp. Level / n / adjOR / (CI) <8 / NR / 1 / n/a 8-<10 / NR / 1.14 / 0.6, 2.3 10-<13 / NR / 1.16 / 0.5, 2.4 ≥ 13 / NR / 1.59 / 0.8, 3.3 Stat Method: Unconditional multiple logistic regression analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		urine arsenic concentration (10-19 years exposure, subjects reported to have ever smoked) (quartiles), (mg/L) x yr. Exp. Level / n / adjOR / (CI) <8 / NR / 1 / n/a 8-<10 / NR / 1.36 / 0.5, 3.9 10-<13 / NR / 1.57 / 0.5, 4.5 ≥ 13 / NR / 2.92 / 1.1, 8.0 Stat Method: Unconditional multiple logistic regression analysis
		urine arsenic concentration (30-39 years exposure, subjects reported to have ever smoked) (quartiles), (mg/L) x yr. Exp. Level / n / adjOR / (CI) <8 / NR / 1 / n/a 8-<10 / NR / 1.86 / 0.4, 9.7 10-<13 / NR / 1.48 / 0.3, 7.4 ≥ 13 / NR / 8.7 / 1.7, 44 Stat Method: Unconditional multiple logistic regression analysis
		urine arsenic concentration (all subjects) (quartiles), (mg/L) x yr. Exp. Level / n / adjOR / (CI) <33 / NR / 1 / n/a 33-<53 / NR / 0.69 / 0.3, 1.5 53-<74 / NR / 0.54 / 0.3, 1.2 ≥ 74 / NR / 1 / 0.5, 2.1 Stat Method: Unconditional multiple logistic regression analysis
		urine arsenic concentration (ever smokers) (quartiles), (mg/L) x yr. Exp. Level / n / adjOR / (CI) <33 / NR / 1 / n/a 33-<53 / NR / 1.95 / 0.7, 5.6 53-<74 / NR / 1.21 / 0.4, 3.7 ≥ 74 / NR / 1.41 / 0.5, 4.3 Stat Method: Unconditional multiple logistic regression analysis
Bates et al. (2004) **Study Type:** case-	**Exposure Surrogate:** drinking water **Exposure Description:** average arsenic	**Outcome: bladder cancer** ***arsenic concentration (excluding proxy wells) (quartiles), µg/L*** Exp. Level / n / adjOR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
control **Location:** Argentina (Cordoba Province) **Population:** Argentinians living in region with high arsenic water concentrations n cases: 114 n control: 114	water concentration estimated for 6-40 years prior to interview based on samples collected from wells near individual's current and past residences **Population-Level Exposure:** 164 µg/L mean	0-50 NR 1 n/a 51-100 NR 1.11 0.3, 3.7 101-200 NR 0.81 0.3, 2.0 >200 NR 0.28 0.1, 1.4 Stat Method: Multivariate conditional logistic regression ***consumption of well water over past 61-70 years, smokers only, µg/L*** Exp. Level / n / adjOR / (CI) No NR 1 n/a Yes NR 2.54 1.0, 6.4 Stat Method: Multivariate unconditional logistic regression (adjusted for highest daily number of cigarettes ever smoked)
Chen et al. (2010b) **Study Type:** cohort (prospective) **Location:** Taiwan region not available **Population:** adult residents of arseniasis-endemic area in northeast n exposed: 5,798 n reference: 2,288 n total: 8,086	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in well water estimated based on concentration measurements from 3,901 samples from 4,584 houses (85.1% of total households) **Population-Level Exposure:** 0.15-3,000 µg/L range	**Outcome: all urinary cancer** ***arsenic concentration in well water, µg/L*** Exp. Level / n / adjRR / (CI) <10 5 1 n/a 10-49.9 8 1.66 0.53, 5.21 50-99.9 5 2.42 0.69, 8.54 100-299.9 8 4.13 1.32, 12.9 ≥ 300 11 7.8 2.64, 23.1 Unknown 8 3.4 1.05, 11.0 Stat Method: Cox proportional hazard regression model **Outcome: urothelial carcinoma** ***arsenic concentration in well water, µg/L*** Exp. Level / n / adjRR / (CI) <10 3 1 n/a 10-49.9 6 1.85 0.45, 7.61 50-99.9 3 2.19 0.43, 11.1 100-299.9 7 5.5 1.39, 21.8 ≥ 300 10 10.8 2.90, 40.3 Unknown 7 4.34 1.06, 17.7 Stat Method: Cox proportional hazard regression model
	Exposure Surrogate: drinking water **Exposure Description:** concentration in well water measured in samples from 85.1% of total households; cumulative	**Outcome: all urinary cancer** ***cumulative arsenic exposure concentration, µg/L-year*** Exp. Level / n / adjRR / (CI) <400 NR 1 n/a 400-<1,000 NR 1.11 0.27, 4.54

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	exposure estimated based on self-reported duration of well water consumption and concentration at current residence when actual concentrations not available **Population-Level Exposure:** 0.15-3,000 µg/L-year range	1,000-<5,000 NR 2.33 0.86, 6.36 5,000-<10,000 NR 3.77 1.13, 12.6 ≥ 10,000 NR 7.49 2.70, 20.8 unknown NR 2.98 0.99, 8.95 Stat Method: Cox proportional hazard regression model **Outcome: urothelial carcinoma** ***cumulative arsenic exposure concentration, µg/L-year*** Exp. Level n adjRR (CI) <400 NR 1 n/a 400-<1,000 NR 1.35 0.22, 8.25 1,000-<5,000 NR 3.2 0.85, 12.1 5,000-<10,000 NR 6.93 1.62, 29.5 ≥ 10,000 NR 12.6 3.40, 46.8 unknown NR 4.65 1.16, 18.7 Stat Method: method not available
Chiou et al. (1995) **Study Type:** cohort (prospective) **Location:** Taiwan (Southwestern coast of Taiwan [Peimen, Hsuechia, Putai, and Ichu townships]) **Population:** BFD patients and healthy residents in arseniasis-endemic townships n exposed: 263 n reference: 2,293 n total: 2,556	**Exposure Surrogate:** drinking water **Exposure Description:** individual exposure estimated using median arsenic levels in artesian well water in each village combined with residential history information gathered during individual interviews **Population-Level Exposure:** 0.78 mg/L median	**Outcome: bladder cancer** ***average arsenic concentration in well water, mg/L*** Exp. Level n adjRR (CI) ≤ 0.05 6 1 n/a 0.05-0.70 7 1.8 0.6, 5.3 >0.71 7 3.3 1.0, 11.1 unknown 9 1.2 0.4, 3.4 Stat Method: Cox proportional hazards regression analysis ***cumulative water arsenic exposure, mg/L-yr*** Exp. Level n adjRR (CI) 0 NR 1 n/a 0.1-19.9 NR 1.57 0.44, 5.55 >20 NR 3.58 1.05, 12.19 Unknown NR 1.25 0.38, 4.12 Stat Method: Cox proportional hazards regression analysis
Chiou et al. (2001a) **Study Type:** cohort (prospective)	**Exposure Surrogate:** drinking water **Exposure Description:** well water samples collected and analyzed from	**Outcome: cancer of urinary organs** ***arsenic concentration in well water, µg/L*** Exp. Level n RR (CI) 0-10.0 3 1 n/a 10.1-50.0 3 1.6 0.3, 8.4

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Location: Taiwan (Lanyang Basin) **Population:** residents of arseniasis-endemic area of northeastern Taiwan consuming well water n exposed: 8,102 n total: 8,102	3,901 (85.1%) households during home interview **Population-Level Exposure:** 0.15-3,590 µg/L range	50.1-100.0 2 2.3 0.4, 14.1 >100.0 7 4.9 1.2, 20.0 Stat Method: Cox proportional hazards regression analysis **Outcome: transitional cell carcinoma** ***arsenic concentration in well water, µg/L*** Exp. Level / n / RR / (CI) 0-10.0 1 1 n/a 10.1-50.0 1 1.9 0.1, 32.2 50.1-100.0 2 8.1 0.7, 98.2 >100.0 5 15.1 1.7, 138.5 Stat Method: Cox proportional hazards regression analysis
Chung et al. (2011) **Study Type:** case-control **Location:** Taiwan (Taipei) **Population:** males and females with urothelial carcinoma identified at hospital; controls from same area with no prior cancer history; most consumed tap water n cases: 170 n control: 402	**Exposure Surrogate:** urine **Exposure Description:** spot urine analyzed; total arsenic = sum of As(III), As(V), MMA(V), and DMA(V); relative proportion of urinary arsenic species calculated by dividing each arsenic species level by total arsenic **Population-Level Exposure:** 26.02 µg/g-creatinine mean	**Outcome: urothelial carcinoma** ***inorganic arsenic percentage (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <2.86 44 1 n/a 2.86 - 6.03 52 1.61 0.91, 2.84 ≥ 6.03 74 1.15 0.66, 2 Stat Method: multiple logistic regression ***total arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <12.15 13 1 n/a 12.15 - 22.10 36 2.8 1.26, 6.21 >22.1 121 6.71 3.14, 14.35 Stat Method: multiple logistic regression
Chung et al. (2012) **Study Type:** cohort (prospective) **Location:** Taiwan (Homei, Fuhsin, Hsinming) **Population:** residents of arseniasis-endemic	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure assessment determined by duration of artesian well water use, history or residence, and historical data; cumulative arsenic exposure derived to reflect long-term arsenic exposure by median well water arsenic (population level exposure reported here) x duration of use	**Outcome: bladder cancer** ***cumulative water arsenic exposure (tertiles), µg/L-year*** Exp. Level / n / adjOR / (CI) <9.1 1 1 n/a 9.1-19.5 18 12.91 1.71, 97.59 ≥ 19.5 19 7.74 0.97, 61.51 Stat Method: Cox proportional hazard model

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
areas n total: 1,563	**Population-Level Exposure:** 9.1-19.5 µg/L-year range	
	Exposure Surrogate: drinking water **Exposure Description:** information on median arsenic level in artesian well water of each village acquired from previous studies carried out in the early 1960s (Lai et al., 1994); some study subjects had moved from one village to another, and there were differences in arsenic concentrations between villages **Population-Level Exposure:** 0.7-0.93 mg/L range	**Outcome: bladder cancer** ***average water arsenic concentration (tertiles), mg/L*** Exp. Level / n / HR / (CI) <0.05 / 1 / 1 / n/a 0.05-0.71 / 15 / 4.35 / 0.56, 33.52 ≥ 0.71 / 22 / 7.22 / 0.95, 55.04 Stat Method: Cox proportional hazard model
	Exposure Surrogate: urine **Exposure Description:** urine samples of 1,078 subjects collected at time of recruitment; all arsenic assays performed within 6 months of sample collection **Population-Level Exposure:** not available	**Outcome: bladder cancer** ***percent DMA in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) ≥ 85.8 / 5 / 1 / n/a 76.13-85.8 / 4 / 0.7 / 0.19, 2.62 <76.13 / 19 / 3.05 / 1.11, 8.37 Stat Method: Cox proportional hazard model ***percent inorganic arsenic in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) <4.22 / 4 / 1 / n/a 4.22-7.86 / 10 / 2.42 / 0.75, 7.79 ≥ 7.86 / 14 / 3.53 / 1.16, 10.77 Stat Method: Cox proportional hazard model ***percent MMA in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) <8.34 / 7 / 1 / n/a 8.34-15.31 / 4 / 0.57 / 0.17, 1.95 ≥ 15.31 / 17 / 1.77 / 0.72, 4.36 Stat Method: Cox proportional hazard model
Chung et al. (2013) **Study Type:** case-	**Exposure Surrogate:** urine **Exposure Description:** spot urine	**Outcome: urinary carcinoma** ***percent DMA in total urinary arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjOR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
control **Location:** Taiwan (Taipei) **Population:** hospital patients with urothelial carcinoma n cases: 191 n control: 364	samples collected at time of recruitment from each individual; detection limits for As(III), DMA(V), MMA(V), and As(V) were 0.02, 0.08, 0.05, and 0.07 µg/L, respectively **Population-Level Exposure:** 12.81-23.3 µg/L range	≥ 91.76 NR 1 n/a 83.56-91.76 NR 2.01 1.22, 2.32 <83.56 NR 3.23 2, 5.21 Stat Method: Multivariate logistic regression ***percent inorganic arsenic in total urinary arsenic concentration (tertiles), µg/L*** Exp. Level n adjOR (CI) <2.76 NR 1 n/a 2.76-5.86 NR 1.07 0.66, 1.74 ≥ 5.86 NR 2.36 1.53, 3.66 Stat Method: Multivariate logistic regression ***percent MMA in total urinary arsenic concentration (tertiles), µg/L*** Exp. Level n adjOR (CI) <3.36 NR 1 n/a 3.36-9.13 NR 0.91 0.57, 1.45 ≥ 9.13 NR 1.76 1.15, 2.71 Stat Method: Multivariate logistic regression ***total urinary arsenic concentration (tertiles), µg/L*** Exp. Level n adjOR (CI) <12.81 NR 1 n/a 12.81-23.3 NR 1.64 0.95, 2.82 ≥ 23.3 NR 4.63 2.80, 7.65 Stat Method: Multivariate logistic regression
Feki-Tounsi et al. (2013) **Study Type:** case-control **Location:** Tunisia (central and southern Tunisia) **Population:** male patients of hospital urology department with symptoms of bladder cancer or benign diseases	**Exposure Surrogate:** blood **Exposure Description:** arsenic concentrations in blood assessed from whole-blood samples, before hospitalization; subjects grouped for analysis above and below median value (0.70 µg/L) **Population-Level Exposure:** 4.98 µg/L mean 14.6SD	**Outcome: bladder cancer** ***blood arsenic concentration, µg/L*** Exp. Level n adjOR (CI) 0.15-0.70 NR 0.18 0.01, 2.95 0.70-167.00 NR 2.44 1.11, 5.35 Stat Method: Multiple logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
n cases: 86 n control: 196		
Ferreccio et al. (2013b) **Study Type:** case-control **Location:** Chile (Regions I and II, Northern Chile) **Population:** residents with bladder or lung cancer in area formerly having arsenic-contaminated drinking water n cases: 538 n control: 640	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime arsenic exposure estimated by linking subject's residence with water arsenic concentration **Population-Level Exposure:** 0-800 µg/L range	**Outcome: bladder cancer** ***water arsenic concentration - never smoker, µg/L*** Exp. Level / n / adjOR / (CI) <11 / 6 / 1 / n/a >355 / 19 / 8.9 / 3.0, 26 Stat Method: Unconditional logistic regression ***water arsenic concentration - smoked >10 cigarettes/day, µg/L*** Exp. Level / n / adjOR / (CI) <11 never smoker / 6 / 1 / n/a <11 / 14 / 4.1 / 1.3, 13 >355 / 33 / 23 / 8.2, 66 Stat Method: Unconditional logistic regression
Hsu et al. (2013a) **Study Type:** cohort (prospective) **Location:** Taiwan (Peimen, Hsuechia, Putai, Ichu townships) **Population:** 3 separate subcohorts of residents of an arseniasis-endemic area n exposed: 1,075 n reference: 535 n total: 2,447	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime cumulative arsenic exposure estimated using median arsenic concentration in village well where study subject lived and duration of exposure; arsenic concentrations in wells obtained from 2 investigations examining more than 38,565 wells across Taiwan; lifetime cumulative arsenic exposure (CAE) estimated using median arsenic concentration in village well where study subject lived and duration of exposure **Population-Level Exposure:** 1-20 mg/L - yr range	**Outcome: urothelial carcinoma** ***cumulative arsenic exposure, mg/L - yr*** Exp. Level / n / HR / (CI) <1.0 / NR / 1 / n/a 1.0-19.9 / NR / 1.43 / 0.76, 2.68 ≥ 20 / NR / 2.97 / 1.58, 5.60 missing / NR / 1.21 / 0.70, 2.69 Stat Method: Cox regression analysis with time-dependent covariates
Huang et al. (2008b) **Study Type:** case-control **Location:** Taiwan	**Exposure Surrogate:** urine **Exposure Description:** single spot arsenic measurement evaluated, including speciation, for each individual	**Outcome: urothelial cancer** ***total urinary arsenic (quartiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <13.09 / NR / 1 / n/a 13.10-20.29 / NR / 1.48 / 0.69, 3.12 20.30-30.59 / NR / 3.22 / 1.62, 6.27 ≥ 30.60 / NR / 6.26 / 3.21, 12.22

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
region not available **Population:** hospital patients with or without urothelial carcinomas n cases: 171 n control: 488	**Population-Level Exposure:** 13.09-30.6 µg/g-creatinine range	Stat Method: Logistic regression
Huang et al. (2008a) **Study Type:** cohort (prospective) **Location:** Taiwan (southwest [Putai township of Chiayi County]) **Population:** adult residents in selected villages n exposed: 573 n reference: 138 n total: 965	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic levels in well water collected in studies conducted in the 1960s, assigned based on self-reported information on residential history **Population-Level Exposure:** 0-0.9 mg/L range	**Outcome: urothelial carcinoma** ***average arsenic concentration in well water, mg/L*** Exp. Level / n / RR / (CI) 0-0.4 / 1 / 1 / n/a 0.41-0.7 / 14 / 5.2 / 0.7, 39.8 0.71-0.9 / 9 / 6.7 / 0.8, 53.4 ≥ 0.9 / 7 / 6.5 / 0.8, 53.1 Stat Method: Cox proportional hazards model
	Exposure Surrogate: drinking water **Exposure Description:** cumulative arsenic exposure determined using self-reported information on residential history and duration of consuming high-arsenic artesian well water; arsenic levels in well water collected in previous studies conducted in the 1960s **Population-Level Exposure:** 0-20 mg/L-yr range	**Outcome: urothelial carcinoma** ***cumulative arsenic exposure index, mg/L-yr*** Exp. Level / n / RR / (CI) 0 / 0 / 1 / n/a 0.1-11.9 / 2 / NR / n/a 12-19.9 / 9 / 4.6 / 1.0, 21.8 ≥ 20 / 20 / 7.9 / 1.7, 37.9 Stat Method: Cox proportional hazards model
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic concentration, including speciation, measured from single sample for each individual **Population-Level Exposure:** 4.29-8.02 % range	**Outcome: urothelial carcinoma** ***inorganic urinary arsenic (tertiles), %*** Exp. Level / n / RR / (CI) <4.29 / NR / 1 / n/a 4.29-8.02 / NR / 1.4 / 0.6, 3.4 ≥ 8.02 / NR / 1.4 / 0.5, 3.6 Stat Method: Cox proportional hazards model
Karagas et al. (2004)	**Exposure Surrogate:** toenails	**Outcome: bladder cancer** ***toenail arsenic concentration, µg/g*** Exp. Level / n / adjOR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: case-control **Location:** United States (NH) **Population:** adult residents with bladder cancer consuming water from private wells containing arsenic and public water systems n cases: 383 n control: 641	**Exposure Description:** toenail arsenic concentration measured from clean samples **Population-Level Exposure:** 0.009-2.484 µg/g range	0.009–0.059 NR 1 n/a 0.060–0.086 NR 1.37 0.96, 1.96 0.087–0.126 NR 1.08 0.74, 1.58 0.127–0.193 NR 1.04 0.66, 1.63 0.194–0.277 NR 1.33 0.71, 2.49 0.278–0.330 NR 0.41 0.11, 1.50 0.331–2.484 NR 1.36 0.63, 2.90 Stat Method: Logistic regression with log transformation of the arsenic exposure variable
Kurttio et al. (1999) **Study Type:** case-control **Location:** Finland region not available **Population:** register-based cohort of Finnish people living outside municipal water system from 1967-1980; 61 bladder cancer cases, 49 kidney cancer cases n cases: 49 n control: 275	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration measured in well-water samples collected Jul-Nov 1996 from locations where individuals lived from 1967-1980 **Population-Level Exposure:**	**Outcome: bladder cancer** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjRR (CI) <.1 NR 1 n/a 0.1-0.5 NR 1.53 0.75, 3.09 ≥ 0.5 NR 2.44 1.11, 5.37 Stat Method: Linear modeling after log transformation
	Exposure Surrogate: drinking water **Exposure Description:** cumulative arsenic dose calculated based on duration of exposure as reported in questionnaire and sampled arsenic concentration in well water; if questionnaire data not available, assumed mean value from the reference cohort for consumption; arsenic concentration in drinking water before and after well-water use was considered null **Population-Level Exposure:** 0.8 mg median	**Outcome: bladder cancer** ***cumulative arsenic dose, mg*** Exp. Level n adjRR (CI) <0.5 NR 1 n/a 0.5-2.0 NR 1.61 0.74, 3.54 ≥ 2.0 NR 1.5 0.71, 3.15 Stat Method: Linear modeling after log transformation
	Exposure Surrogate: drinking water	**Outcome: bladder cancer** ***daily dose of arsenic, µg/day***

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Description: daily dose of arsenic estimated from sampled arsenic concentration in well water (collected and measured 1996 from locations where individuals lived from 1967-1980) and reported consumption of well water from the 1970s; if questionnaire data not available assumed mean value from the reference cohort for consumption; arsenic concentration in drinking water before and after well-water use considered null **Population-Level Exposure:** 0.2 µg/day median	Exp. Level / n / adjRR / (CI) <0.2 / NR / 1 / n/a 0.2-1.0 / NR / 1.34 / 0.66, 2.69 ≥ 1.0 / NR / 1.84 / 0.84, 4.03 Stat Method: Linear modeling after log transformation
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2,203 n total: 2,203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: bladder and other urinary organs cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 1.18 / n/a 1,000-4,999 / NR / NR / n/a ≥ 5,000 / NR / 1.1 / n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 0.36 / n/a 1,000-4,999 / NR / NR / n/a ≥ 5,000 / NR / 0.95 / n/a Stat Method: standardized mortality ratios
Meliker et al. (2010) **Study Type:** case-control **Location:** United States (Southeastern Michigan [11 counties]) **Population:** residents in study area with bladder cancer	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime exposure to arsenic calculated from measures at current residence and modeled estimates for past residences based on historical sources **Population-Level Exposure:** 1-10 µg/L range	**Outcome: bladder cancer** ***time-weighted average (TWA) arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) continuous (per 5 µg/L increase) / NR / 1.05 / 0.92, 1.20 <1 / NR / 1 / n/a 1-10 / NR / 0.84 / 0.63, 1.12 >10 / NR / 1.1 / 0.65, 1.86 Stat Method: Unconditional logistic regression; multivariate-adjusted analyses
	Exposure Surrogate: drinking water	**Outcome: bladder cancer**

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
diagnosed between 2000 and 2004 plus controls n cases: 411 n control: 566	**Exposure Description:** lifetime exposure to arsenic estimated using measures at current residence and modeled estimates for past residence using historical sources **Population-Level Exposure:** 1-10 µg/day range	***time-weighted average (TWA) arsenic intake from water (µg/day), µg/day*** Exp. Level / n / adjOR / (CI) continuous (per 5 µg/day increase) / NR / 1.01 / 0.92, 1.12 <1 / NR / 1 / n/a 1-10 / NR / 0.83 / 0.62, 1.11 >10 / NR / 1.01 / 0.62, 1.64 Stat Method: Unconditional logistic regression; multivariate-adjusted analyses
Michaud et al. (2004) **Study Type:** case-control (nested) **Location:** Finland (southwest) **Population:** cohort of Finnish male smokers aged 50–69 years enrolled in Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study n cases: 280 n control: 293	**Exposure Surrogate:** toenails **Exposure Description:** intact and pulverized toenails cleaned prior to analysis for arsenic; detection limit varied across samples due to contamination and samples with nondetectable arsenic and high detection limits >0.09 µg/g excluded (51/331 cases, 38/331 controls) **Population-Level Exposure:** 0.05-0.161 µg/g range	**Outcome: bladder cancer** ***toenail arsenic concentration (categorized by percentiles), µg/g*** Exp. Level / n / adjOR / (CI) ≤ 50%ile (<0.105) / NR / 1 / n/a 50.1-75%ile (0.105-0.160) / NR / 1.1 / 0.73, 1.64 75.1-90%ile (0.161-0.259) / NR / 0.93 / 0.56, 1.54 90.1-95%ile (0.260-0.399) / NR / 1.38 / 0.68, 2.80 95.1-100%ile (>0.399) / NR / 1.14 / 0.52, 2.51 Stat Method: Unconditional logistic regression ***toenail arsenic concentration (quartiles), µg/g*** Exp. Level / n / adjOR / (CI) <0.050 / NR / 1 / n/a 0.050-0.105 / NR / 1.09 / 0.68, 1.74 0.106-0.161 / NR / 0.13 / 0.71, 1.8 >0.161 / NR / 1.13 / 0.7, 1.81 Stat Method: Unconditional logistic regression
Pu et al. (2007) **Study Type:** case-control **Location:** Taiwan	**Exposure Surrogate:** urine **Exposure Description:** single spot urine arsenic measurement analyzed and inorganic arsenic and its metabolites quantified; exposure groups divided in	**Outcome: urothelial carcinoma** ***urinary arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) ≤ 15.4 / 24 / 1 / n/a 15.5-26.4 / 44 / 1.6 / 0.8, 3.0 >26.4 / 109 / 3.2 / 1.8, 5.9

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(Taipei) **Population:** adult urothelial carcinoma (UC) patients and non-UC patients in area where maximum contaminant level for arsenic in public water reduced from 50 µg/L to 10 µg/L in 2000 n cases: 177 n control: 313	tertiles based on urinary arsenic measured in control population **Population-Level Exposure:** 15.4-26.4 µg/g-creatinine range	Stat Method: Multiple logistic regression
Sawada et al. (2013) **Study Type:** cohort (prospective) **Location:** Japan (Iwate, Akita, Nagano, Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90,378	**Exposure Surrogate:** diet **Exposure Description:** detailed questionnaire on food intake/frequency; average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	**Outcome: bladder cancer** ***inorganic arsenic intake (females; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.6 / 6 / 1 / n/a 53.7 / 10 / 1.96 / 0.7, 5.53 62.6 / 10 / 2.06 / 0.72, 5.87 105.7 / 7 / 1.54 / 0.5, 4.73 Stat Method: Multivariate regression ***inorganic arsenic intake (males; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.5 / 28 / 1 / n/a 54.7 / 41 / 1.45 / 0.89, 2.37 63.5 / 26 / 0.89 / 0.51, 1.55 99.1 / 46 / 1.56 / 0.95, 2.55 Stat Method: Multivariate regression
Steinmaus et al. (2003) **Study Type:** case-control **Location:** United States (Kings County, CA; 7 counties western NV) **Population:** adult residents from counties with historically high	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure for each subject determined using residence-specific water arsenic measurements from historical and recent records combined with residential history and self-reported intake information; analysis methods not described **Population-Level Exposure:** 6.4-82.8 mg range	**Outcome: bladder cancer** ***cumulative arsenic concentration in drinking water (mg), 40-year lag (tertiles), mg*** Exp. Level / n / adjOR / (CI) <6.4 / 153 / 1 / n/a 6.4 - 82.8 / 9 / 1.63 / 0.64, 4.13 >82.8 / 19 / 1.4 / 0.73, 2.70 Stat Method: Cochran-Armitage test using category means

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
drinking water arsenic and nearby counties n cases: 181 n control: 328		
Steinmaus et al. (2013) **Study Type:** case-control **Location:** Chile (Antofagasta) **Population:** residents with lung cancer or bladder cancer who were formerly exposed to high arsenic levels in drinking water n cases: 538 n control: 640	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentrations for each city or town in the study area collected from government agencies, research studies, and water suppliers; subjects self-reported daily water intake **Population-Level Exposure:** 1,578-12,841 µg/L - yr range	**Outcome: bladder cancer** ***cumulative arsenic concentration: all years (quartiles), µg/L - yr*** Exp. Level / n / adjOR / (CI) <1,578 / 34 / 1 / n/a 1,578-4,876 / 33 / 0.86 / 0.49, 1.52 4,877-12,841 / 78 / 2.97 / 1.76, 5.02 >12,841 / 87 / 5.27 / 2.86, 9.70 Stat Method: Unconditional logistic regression ***cumulative arsenic concentration: before 1971 (quartiles), µg/L - yr*** Exp. Level / n / adjOR / (CI) <372 / 34 / 1 / n/a 372-2,464 / 32 / 1.03 / 0.59, 1.8 2,465–10,319 / 78 / 3.4 / 2.05, 5.65 >10,319 / 88 / 6.33 / 3.54, 11.32 Stat Method: Unconditional logistic regression ***cumulative arsenic intake: all years (quartiles), ug*** Exp. Level / n / adjOR / (CI) <2,438 / 31 / 1 / n/a 2,438-8,214 / 42 / 1.14 / 0.65, 1.99 8,215-19,093 / 58 / 2.58 / 1.46, 4.56 >19,093 / 101 / 7.9 / 4.45, 14.01 Stat Method: Unconditional logistic regression ***cumulative arsenic intake: before 1971 (quartiles), ug*** Exp. Level / n / adjOR / (CI) <576 / 35 / 1 / n/a 576–4,429 / 34 / 1.11 / 0.64, 1.94 4,430–14,347 / 71 / 2.99 / 1.80, 4.97 >14,347 / 92 / 6.82 / 3.92, 11.87 Stat Method: Unconditional logistic regression ***lifetime average arsenic concentration: all years***

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		(quartiles), µg/L Exp. Level / n / adjOR / (CI) <26 / 33 / 1 / n/a 26-79 / 33 / 0.92 / 0.52, 1.61 80-197 / 71 / 2.62 / 1.53, 4.50 >197 / 95 / 6 / 3.38, 10.64 Stat Method: Unconditional logistic regression
		lifetime average arsenic concentration: before 1971 (quartiles), µg/L Exp. Level / n / adjOR / (CI) <11 / 28 / 1 / n/a 11-90 / 37 / 1.36 / 0.78, 2.37 91-335 / 78 / 3.87 / 2.25, 6.64 >335 / 89 / 6.5 / 3.69, 11.43 Stat Method: Unconditional logistic regression
		lifetime daily average arsenic intake: all years (quartiles), µg/day Exp. Level / n / adjOR / (CI) >41 / 32 / 1 / n/a 41-136 / 39 / 1.08 / 0.62, 1.87 137-307 / 64 / 3.06 / 1.75, 5.35 >307 / 97 / 5.85 / 3.41, 10.05 Stat Method: Unconditional logistic regression
		lifetime daily average arsenic intake: before 1971 (quartiles), µg/day Exp. Level / n / adjOR / (CI) <21 / 31 / 1 / n/a 21-159 / 35 / 1.21 / 0.69, 2.11 160-525 / 70 / 3.15 / 1.84, 5.38 >525 / 96 / 6.76 / 3.97, 11.51 Stat Method: Unconditional logistic regression
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho)	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic	**Outcome: urinary cancer** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 / 0 / 0 / 0, 12.50 0.05-0.99 / 0 / 0 / 0, 47.05 ≥ 1 / 3 / 31.18 / 8.82, 91.75 Stat Method: Cox proportional hazard

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Population: adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	
Wu et al. (2012a) **Study Type:** case-control **Location:** Taiwan region not available **Population:** urothelial cancer patients at National Taiwan University Hospital diagnosed 2007-2009 and controls receiving health examinations at one of two Taipei hospitals n cases: 137 n control: 137	**Exposure Surrogate:** urine **Exposure Description:** single spot urine sample collected from each participant at time of recruitment; total arsenic exposure calculated as sum of inorganic arsenic (As[III] + As(V), MMA, and DMA) and normalized against urinary creatinine levels; LOD for As(III), DMA(V), MMA(V), and As(V) = 0.02, 0.06, 0.07, and 0.10 µg/L, respectively **Population-Level Exposure:** not available	**Outcome: urothelial carcinoma** ***total urinary arsenic, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) ≤ 11.38 / 14 / 1 / n/a >11.38 / 57 / 4.24 / 1.92, 9.33 Stat Method: Multivariate logistic regression; linear trend test
Wu et al. (2013) **Study Type:** case-control **Location:** Taiwan, Province Of China (Taipei) **Population:** hospital patients with urothelial carcinoma n cases: 300 n control: 594	**Exposure Surrogate:** urine **Exposure Description:** 50 mL sample of spot urine collected at recruitment; recovery rate for arsenic species ranged from 93.8% to 102.2% **Population-Level Exposure:** 11.74-20.94 µg/g-creatinine range	**Outcome: urothelial carcinoma (UC)** ***total arsenic for each SD (14.45 µg/g-creatinine) increase, IL-8 TA genotype, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) continuous / NR / 1.46 / 1.15, 1.85 Stat Method: Multivariate logistic regression ***total arsenic for each SD (14.45 µg/g-creatinine) increase, IL-8 TT genotype, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) continuous / 188 / 1.75 / 1.45, 2.11 Stat Method: Multivariate logistic regression ***total arsenic for each SD (14.45 µg/g-creatinine) increase, TNF-alpha GG genotype, µg/g-creatinine*** Exp. Level / n / adjOR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		continuous 249 1.73 1.48, 2.03 Stat Method: Multivariate logistic regression
		urinary total arsenic, µg/g-creatinine Exp. Level / n / adjOR / (CI) ≤ 11.74 / 44 / 1 / n/a 11.74 to 20.94 / 63 / 1.42 / 0.9, 2.25 >20.94 / 192 / 4.13 / 2.69, 6.35 Stat Method: Multivariate logistic regression

--: not reported; n: number of cases (when presented in Results column)

5.1.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Bladder Effects

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5.2 Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Bosnjak et al. (2008) **Study Type:** cross-sectional **Location:** Croatia (Andrijasevci) **Population:** adult residents of village with history of higher than average arsenic in drinking water n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from single sample for each individual **Population-Level Exposure:** 627.72 µg/g-creatinine mean, 199.5-1,206.29 µg/g-creatinine range	**Outcome: markers of cardiovascular disease (serum total bilirubin, antibodies to Hsp60 and folate)** ***urinary arsenic concentration, µg/g-creatinine*** non-significant outcomes include: BMI, B9, Hsp60, Hsp70, Hsp70 antibodies, glucose, bilirubin, CRP, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, homocysteine
Burgess et al. (2013) **Study Type:** cross-sectional **Location:** United States, Mexico (Arizona, Sonora) **Population:** adult residents of communities with relatively high drinking water arsenic levels n cases: 377 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration determined from self-reported usage of all water sources consumed for drinking weighted by frequency of use of each source; arsenic levels measured from all reported drinking water sources **Population-Level Exposure:** 7.65 µg/L geo mean, 6.8-8.63 µg/L 95% CI lower	**Outcome: matrix metalloproteinase 9** ***drinking water arsenic concentration, µg/L*** Exp. Level — n — corr coeff — (CI) drinking water total arsenic — NR — 0.135 — n/a Stat Method: multivariable linear mixed model
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic intake calculated as the drinking water arsenic concentration multiplied by the average volume of drinking water consumed daily	**Outcome: matrix metalloproteinase 9** ***drinking water arsenic intake, µg/day*** Exp. Level — n — corr coeff — (CI) drinking water intake — NR — 0.072 — n/a Stat Method: multivariable linear mixed

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
	Population-Level Exposure: 2.47 µg/day geo mean, 1.99-3.07 µg/day 95% CI lower	model
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic sum of species calculated as the sum of As(III), As(V), MMA(V), and DMA(V) **Population-Level Exposure:** 18.44 µg/L geo mean, 18.86-20.17 µg/L 95% CI lower	**Outcome: matrix metalloproteinase 9** ***urinary arsenic sum of species, µg/L*** Exp. Level | n | corr coeff | (CI) urinary total arsenic | NR | 0.121 | n/a Stat Method: multivariable linear mixed model
Chen et al. (2013a) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) participants n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** at baseline, water samples from 10,971 tube wells collected and analyzed for total arsenic **Population-Level Exposure:** 81.1 µg/L mean	**Outcome: carotid intima-media thickness (cIMT)** ***baseline well water arsenic concentration, µg/L*** Exp. Level | n | adjBeta | (CI) continuous | NR | 5.1 | -0.2, 10.3 Stat Method: multiple linear regression
	Exposure Surrogate: urine **Exposure Description:** spot urine samples collected at baseline and at all follow-up visits; total arsenic concentration measured **Population-Level Exposure:** 259.5 µg/g-creatinine mean	**Outcome: carotid intima-media thickness (cIMT)** ***baseline urinary arsenic concentration, µg/g-creatinine*** Exp. Level | n | adjBeta | (CI) continuous | NR | 11.7 | 1.8, 21.6 Stat Method: multiple linear regression
Chen et al. (2012b) **Study Type:** cross-sectional **Location:** Taiwan, Province Of China (Nantou County) **Population:** rural residents of Taiwan n cases: n/a	**Exposure Surrogate:** urine **Exposure Description:** spot morning urine samples collected into polypropylene containers throughout study period **Population-Level Exposure:** 7.7 µg/g-creatinine mean 14.8SD	**Outcome: hypertension** ***urinary arsenic concentration (quartiles), µg/g-creatinine*** Exp. Level | n | adjOR | (CI) Q1 (<1.4) | 21 | 1 | n/a Q2 (1.4-4.3) | 32 | 2.1 | 1.0, 4.4 Q3 (4.3-8.0) | 24 | 1.2 | 0.6, 2.6 Q4 (>8.0) | 37 | 3 | 1.4, 6.3 Stat Method: unconditional logistic regression **Outcome: MnSOD and OGG1 genotyping** ***urinary arsenic concentration (quartiles), µg/g-creatinine***

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
n control: n/a		arsenic not significantly associated with MnSOD and OGG1 genotyping **Outcome: other biochemical parameters (i.e., triglyceride, cholesterol, uric acid)** ***urinary arsenic concentration (quartiles), µg/g-creatinine*** significant ORs for ≥ 150 mg/dl triglyceride and ≥ 200 mg/dl cholesterol; otherwise not significant
Chen et al. (1996) **Study Type:** cohort (prospective) **Location:** Taiwan (Southwest coast: Peimen, Hsuechia, Putai, Ichu, Yensui, Hsiaying townships) **Population:** adults and children living in arseniasis-endemic townships n exposed: 263 n reference: 2,293 n total: 2,556	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated as the drinking water arsenic concentration multiplied by self-reported years living in a particular village and added across individual's lifetime; arsenic levels in well water collected in previous studies conducted in the 1960s **Population-Level Exposure:** 0.01-1.75 mg/L - yr range	**Outcome: ischemic heart disease (ISHD)** ***cumulative water arsenic exposure, mg/L - yr*** Exp. Level / n / adjRR / (CI) 0 / NR / 1 / n/a 0.1-9.9 / NR / 2.2 / 9.46, 10.16 10.0-19.9 / NR / 3.33 / 0.83, 13.45 ≥ 20.0 / NR / 4.9 / 1.36, 17.68 Stat Method: Cox proportional-hazards regression analysis
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic concentrations determined using self-reported information on residential history; arsenic levels in well water collected in previous studies conducted in the 1960s **Population-Level Exposure:** 0.01-1.75 mg/L range	**Outcome: ischemic heart disease (ISHD)** ***drinking water arsenic concentration, mg/L*** Exp. Level / n / adjRR / (CI) 0 / NR / 1 / n/a 0.01-0.50 / NR / 2.8 / n/a ≥ 0.51 / NR / 4.1 / n/a Stat Method: Cox proportional-hazards regression analysis
Chen et al. (2006b) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** healthy,	**Exposure Surrogate:** drinking water **Exposure Description:** at baseline, samples of water collected from 5,967 contiguous wells in the study area **Population-Level Exposure:** 0.5-439 µg/L range	**Outcome: carotid artery intima-medial thickness (IMT) >0.75 mm** ***baseline well arsenic (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) 0.5-11 / 4 / 1 / n/a 12-144 / 3 / 1.1 / 0.2, 6.3 145-439 / 6 / 2.1 / 0.4, 10.5 Stat Method: unconditional logistic regression model
	Exposure Surrogate: drinking water	**Outcome: carotid artery intima-medial thickness**

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
normotensive individuals participating in the ongoing Health Effects of Arsenic Longitudinal Study (HEALS) n total: 66	**Exposure Description:** at baseline, samples of water collected from 5,967 contiguous wells in the study area; cumulative arsenic index (CAI) calculated as the product of amount of water consumed per day (L/day), concentration of arsenic in well(s) (g/L), and duration(s) of well usage (days) **Population-Level Exposure:** 5.3-4,564.1 mg range	**(IMT) >0.75 mm** ***cumulative arsenic index at baseline (tertiles), mg*** Exp. Level / n / adjOR / (CI) 5.3-92.3 / 5 / 1 / n/a 92.4-1,301.5 / 1 / 0.2 / 0.1, 1.7 1,301.6-4,564.1 / 7 / 1.6 / 0.4, 7.5 Stat Method: unconditional logistic regression model
	Exposure Surrogate: urine **Exposure Description:** samples of urine collected at both baseline and follow-up visits **Population-Level Exposure:** 6-209 µg/L range	**Outcome: carotid artery intima-medial thickness (IMT) >0.75 mm** ***baseline urinary total arsenic (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) 6-49 / 4 / 1 / n/a 103-209 / 4 / 2.1 / 0.3, 13.1 >209 / 5 / 6 / 0.5, 80.7 Stat Method: unconditional logistic regression model
Chen et al. (2007b) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study, adult participants n cases: 10,910 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration calculated from well water samples for a set of 5,966 contiguous wells in the area **Population-Level Exposure:** 0.1-864 µg/L range	**Outcome: diastolic hypertension** ***time-weighted well arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 0.96 / 0.77, 1.20 40.9-91.0 / NR / 1.01 / 0.81, 1.25 91.1-176.0 / NR / 0.93 / 0.75, 1.16 176.1-864.0 / NR / 0.97 / 0.78, 1.20 Stat Method: Linear regression analysis; logistic regression analysis ***time-weighted well arsenic concentration (≥ 5 years of known level), µg/L*** Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 0.94 / 0.72, 1.22 40.9-91.0 / NR / 1.07 / 0.83, 1.38 91.1-176.0 / NR / 0.93 / 0.72, 1.20 176.1-864.0 / NR / 1 / 0.78, 1.28 Stat Method: Linear regression analysis; logistic regression analysis **Outcome: general hypertension**

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		time-weighted well arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 1.1 / 0.90, 1.33 40.9-91.0 / NR / 1.03 / 0.85, 1.25 91.1-176.0 / NR / 1.01 / 0.83, 1.22 176.1-864.0 / NR / 1.02 / 0.84, 1.23 Stat Method: Linear regression analysis; logistic regression analysis
		time-weighted well arsenic concentration (≥ 5 years of known level), µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 1.06 / 0.84, 1.34 40.9-91.0 / NR / 1.12 / 0.89, 1.41 91.1-176.0 / NR / 1.03 / 0.82, 1.30 176.1-864.0 / NR / 1.05 / 0.84, 1.31 Stat Method: Linear regression analysis; logistic regression analysis
		Outcome: pulse blood pressure
		time-weighted well arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 1.39 / 1.14, 1.71 40.9-91.0 / NR / 1.21 / 0.99, 1.49 91.1-176.0 / NR / 1.19 / 0.97, 1.45 176.1-864.0 / NR / 1.19 / 0.97, 1.46 Stat Method: Linear regression analysis; logistic regression analysis
		time-weighted well arsenic concentration (≥ 5 years of known level), µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 1.5 / 1.16, 1.91 40.9-91.0 / NR / 1.34 / 1.04, 1.73 91.1-176.0 / NR / 1.35 / 1.05, 1.71 176.1-864.0 / NR / 1.24 / 0.97, 1.59 Stat Method: Linear regression analysis; logistic regression analysis
		Outcome: systolic hypertension
		time-weighted well arsenic concentration (≥ 5

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		years of known level), µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 1.35 / 1.02, 1.77 40.9-91.0 / NR / 1.28 / 0.97, 1.69 91.1-176.0 / NR / 1.3 / 0.99, 1.72 176.1-864.0 / NR / 1.12 / 0.85, 1.47 Stat Method: Linear regression analysis; logistic regression analysis
		time-weighted well arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-40.8 / NR / 1.39 / 1.10, 1.75 40.9-91.0 / NR / 1.21 / 0.96, 1.54 91.1-176.0 / NR / 1.28 / 1.01, 1.62 176.1-864.0 / NR / 1.13 / 0.90, 1.44 Stat Method: Logistic regression analysis
Chen et al. (2011b) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study, adult participants number of subjects not reported	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration calculated from well water samples for a set of 5,966 contiguous wells in the area **Population-Level Exposure:** 99 µg/L mean	**Outcome: death from cerebrovascular disease** ***drinking water arsenic concentration at baseline, µg/L*** Exp. Level / n / HR / (CI) 3.7 / NR / 1 / n/a 35.9 / NR / 1.35 / 0.75, 2.43 102.5 / NR / 1.2 / 0.63, 2.27 265.7 / NR / 1.07 / 0.54, 2.12 Stat Method: Cox proportional hazards regression **Outcome: death from disease of circulatory system** ***drinking water arsenic concentration at baseline, µg/L*** Exp. Level / n / HR / (CI) 3.7 / NR / 1 / n/a 35.9 / NR / 1.21 / 0.8, 1.84 102.5 / NR / 1.24 / 0.80, 1.93 265.7 / NR / 1.46 / 0.96, 2.20 Stat Method: Cox proportional hazards regression **Outcome: death from ischemic heart disease** ***drinking water arsenic concentration at baseline, µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / HR / (CI) 3.7 / NR / 1 / n/a 35.9 / NR / 1.22 / 0.56, 2.65 102.5 / NR / 1.49 / 0.70, 3.19 265.7 / NR / 1.94 / 0.99, 3.84 Stat Method: Cox proportional hazards regression
		Outcome: death from ischemic heart disease and other forms of heart disease
		drinking water arsenic concentration at baseline, µg/L Exp. Level / n / HR / (CI) 3.7 / NR / 1 / n/a 35.9 / NR / 1.22 / 0.65, 2.32 102.5 / NR / 1.35 / 0.71, 2.57 265.7 / NR / 1.92 / 1.07, 3.43 Stat Method: Cox proportional hazards regression
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic concentration measured from single baseline sample for each individual **Population-Level Exposure:** 6.6-1,100 µg/g-creatinine range	**Outcome: death from cerebrovascular disease**
		urinary arsenic concentration at baseline, µg/g-creatinine Exp. Level / n / HR / (CI) 68.5 / NR / 1 / n/a 150.6 / NR / 0.96 / 0.52, 1.79 264.9 / NR / 1.6 / 0.88, 2.90 641.5 / NR / 1.03 / 0.53, 2.03 Stat Method: Cox proportional hazards regression
		Outcome: death from disease of circulatory system
		urinary arsenic concentration at baseline, µg/g-creatinine Exp. Level / n / HR / (CI) 68.5 / NR / 1 / n/a 150.6 / NR / 1.15 / 0.77, 1.72 264.9 / NR / 1.56 / 1.03, 2.38 641.5 / NR / 1.55 / 1.01, 2.37 Stat Method: Cox proportional hazards regression
		Outcome: death from ischemic heart disease
		urinary arsenic concentration at baseline, µg/g-

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		creatinine Exp. Level / n / HR / (CI) 68.5 / NR / 1 / n/a 150.6 / NR / 1.29 / 0.66, 2.51 264.9 / NR / 1.47 / 0.72, 3.01 641.5 / NR / 1.9 / 0.91, 3.98 Stat Method: Cox proportional hazards regression
		Outcome: death from ischemic heart disease and other forms of heart disease
		urinary arsenic concentration at baseline, µg/g-creatinine Exp. Level / n / HR / (CI) 68.5 / NR / 1 / n/a 150.6 / NR / 1.29 / 0.74, 2.27 264.9 / NR / 1.53 / 0.83, 2.82 641.5 / NR / 2.06 / 1.14, 3.72 Stat Method: Cox proportional hazards regression
Chen et al. (2013c) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) participants n exposed: 237 n reference: 1,474 n total: 1,711	**Exposure Surrogate:** drinking water **Exposure Description:** at baseline, water samples from 10,971 contiguous wells collected and analyzed for total arsenic; exposure in quartiles **Population-Level Exposure:** 0.1-790 µg/L range	**Outcome: PR prolongation**
		well water arsenic concentration, µg/L no apparent association of either baseline well water arsenic or baseline urinary arsenic with PR prolongation in men or women
		Outcome: QRS prolongation
		well water arsenic concentration, µg/L no apparent association of either baseline well water arsenic or baseline urinary arsenic with QRS prolongation in men or women
		Outcome: QTc prolongation
		well water arsenic concentration (females), µg/L Exp. Level / n / adjOR / (CI) continuous / NR / 1.24 / 1.05, 1.47 Stat Method: unconditional logistic regression
		well water arsenic concentration (females; quartiles), µg/L Exp. Level / n / adjOR / (CI) 0.1-9 / 40 / 1 / n/a 9.5-57 / 49 / 1.22 / 0.77, 1.93 58-144 / 35 / 0.89 / 0.54, 1.46 145-790 / 55 / 1.61 / 1.00, 2.58

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: unconditional logistic regression
		well water arsenic concentration (males), µg/L Exp. Level / n / adjOR / (CI) continuous / NR / 0.99 / 0.73, 1.33 Stat Method: unconditional logistic regression
		well water arsenic concentration (males; quartiles), µg/L Exp. Level / n / adjOR / (CI) 0.1-9 / 17 / 1 / n/a 9.5-57 / 14 / 0.82 / 0.39, 1.75 58-144 / 14 / 0.85 / 0.40, 1.82 145-790 / 13 / 0.76 / 0.34, 1.69 Stat Method: unconditional logistic regression
	Exposure Surrogate: urine **Exposure Description:** spot urine samples collected from 95.6, 94.5, and 91.2% of original cohort participants at baseline, first follow-up, and second follow-up visits, respectively; adjusted for urinary creatinine **Population-Level Exposure:** 1-4306 µg/g-creatinine range	**Outcome: QTc prolongation**
		urinary arsenic concentration (females), µg/g-creatinine Exp. Level / n / adjOR / (CI) continuous / NR / 1.24 / 1.01, 1.53 Stat Method: unconditional logistic regression
		urinary arsenic concentration (females; quartiles), µg/g-creatinine Exp. Level / n / adjOR / (CI) 1-101 / 33 / 1 / n/a 102-187 / 43 / 1.31 / 0.80, 2.16 188-327 / 44 / 1.43 / 0.87, 2.36 328-4,306 / 51 / 1.69 / 1.00, 2.86 Stat Method: unconditional logistic regression
		urinary arsenic concentration (males), µg/g-creatinine Exp. Level / n / adjOR / (CI) continuous / NR / 0.86 / 0.49, 1.51 Stat Method: unconditional logistic regression
		urinary arsenic concentration (males; quartiles), µg/g-creatinine Exp. Level / n / adjOR / (CI) 7-101 / 18 / 1 / n/a 102-187 / 13 / 0.76 / 0.36, 1.63 188-327 / 14 / 0.83 / 0.39, 1.76 328-4,306 / 13 / 1.01 / 0.44, 2.36 Stat Method: unconditional logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Chiou et al. (1997) **Study Type:** cross-sectional **Location:** Taiwan (Lanyang Basin) **Population:** adults living in arseniasis-endemic townships n cases: 8,102 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of use **Population-Level Exposure:** 1-5 mg/L-yr range	**Outcome: cerebral Infarction** ***cumulative drinking water arsenic exposure, mg/L-yr*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-4.9 / NR / 2.66 / 1.21, 5.83 >5.0 / NR / 3.39 / 1.42, 8.11 Stat Method: Multiple logistic regression **Outcome: cerebrovascular disease** ***cumulative drinking water arsenic exposure, mg/L-yr*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-4.9 / NR / 2.26 / 1.23, 4.15 >5.0 / NR / 2.69 / 1.35, 5.38 Stat Method: Multiple logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic exposure calculated from single well water sample collected from each household **Population-Level Exposure:** 0.1-300 µg/L range	**Outcome: cerebral Infarction** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-50 / NR / 3.38 / 1.57, 7.27 50.1-299.9 / NR / 4.47 / 2.03, 9.87 ≥ 300 / NR / 6.9 / 2.91, 16.38 Stat Method: Multiple logistic regression **Outcome: cerebrovascular disease** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-50 / NR / 2.53 / 1.47, 4.35 50.1-299.9 / NR / 2.78 / 1.55, 4.97 ≥ 300 / NR / 3.6 / 1.83, 7.11 Stat Method: Multiple logistic regression
Chiou et al. (2005) **Study Type:** cohort (retrospective) **Location:** Taiwan (southwestern: Tainan County (Yenshui,	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration as reported by the National Taiwan University Group; median concentration used as surrogate if village had multiple wells	**Outcome: microvascular disease** ***drinking water arsenic concentration - microvascular diseases, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1.366 / n/a Stat Method: Logistic regression model

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Beimen, and Shuechia townships), Chiayi County (Putai and Yichu townships)) **Population:** adults and children living in arseniasis-endemic townships n total: 28,499	**Population-Level Exposure:** 0.1-0.6 mg/L range	
Guha Mazumder et al. (2012) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** adults and children likely exposed to higher than average arsenic in drinking water n cases: 208 n control: 100	**Exposure Surrogate:** drinking water **Exposure Description:** present and previous (if available) drinking and cooking water source samples collected for each individual; cumulative arsenic exposure calculated as the drinking water arsenic concentration of each well used multiplied by self-reported duration of use and added across individual's lifetime **Population-Level Exposure:** 0-24.98 mg/L - yr range	**Outcome: hypertension** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / 20 / 1 / n/a 0-4.5 / 37 / 1.65 / 1.02, 6.14 >4.5 / 24 / 2.07 / 0.64, 6.57 Stat Method: multivariate logistic regression
	Exposure Surrogate: hair **Exposure Description:** arsenic concentration measured from a cleaned bunch of hair samples for each individual **Population-Level Exposure:** 0.06-7.51 mg/kg range	**Outcome: hypertension** ***hair arsenic concentration, mg/kg*** Exp. Level / n / adjOR / (CI) 0-0.18 / 12 / 1 / n/a 0.19-2.0 / 51 / 1.37 / 0.65, 3.81 >2.0 / 18 / 2.39 / 0.57, 10.00 Stat Method: multivariate logistic regression
Guo et al. (2007) **Study Type:** cross-sectional **Location:** Mongolia region not available **Population:** residents of villages in the Hetao	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic samples were taken from 94 water sources, including wells; detection limit not specified, but authors note reliability of the method at <10 µg/L; arsenic exposure determined by location of village	**Outcome: hypertension** ***water arsenic concentration, µg/L*** Exp. Level / n / Prev / (CI) ≤ 50 µg/L / NR / 0.53 / n/a >50 µg/L / NR / 8.09 / n/a Stat Method: not reported

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Plain, Inner Mongolia n cases: 680 n control: 189	**Population-Level Exposure:** 50-1,860 µg/L range	
Hawkesworth et al. (2013) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** children in Maternal and Infant Nutrition Interventions in Matlab (MINIMat) cohort n total: 2,499	**Exposure Surrogate:** maternal urine **Exposure Description:** spot urine samples from participating women collected at 8 and 30 weeks gestation; log transformed as continuous variable for analysis; median maternal urinary arsenic was 80 µg/L (10th, 90th percentile: 24, 383 µg/L) at week 8 of gestation and 83 µg/L (10th, 90th: 26, 415 µg/L) at week 30 **Population-Level Exposure:** 80 mg/L median	**Outcome: diastolic blood pressure** ***maternal urinary arsenic concentration (combined), mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 2.91 / 0.41, 5.42 Stat Method: linear regression ***maternal urinary arsenic concentration week 30, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 2.45 / -0.03, 4.94 Stat Method: linear regression ***maternal urinary arsenic concentration week 8, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 1.75 / -0.73, 4.22 Stat Method: linear regression **Outcome: systolic blood pressure** ***maternal urinary arsenic concentration (combined), mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 3.69 / 0.74, 6.63 Stat Method: linear regression ***maternal urinary arsenic concentration week 30, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 3.56 / 0.62, 6.5 Stat Method: linear regression ***maternal urinary arsenic concentration week 8, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 1.45 / -1.51, 4.41 Stat Method: linear regression
	Exposure Surrogate: urine **Exposure Description:** urine samples collected from participating children at	**Outcome: diastolic blood pressure** ***infant urinary arsenic concentration 18 months, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 2.75 / -3.09, 8.59

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
	18 months of age; log transformed as continuous variable for analysis; median urinary arsenic was 34 µg/L (10th, 90th percentile: 12, 154 µg/L) **Population-Level Exposure:** 34 mg/L median	Stat Method: linear regression **Outcome: systolic blood pressure** ***infant urinary arsenic concentration 18 months, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 8.25 / 1.37, 15.1 Stat Method: linear regression
Hsieh et al. (2008a) **Study Type:** case-control (nested) **Location:** Taiwan (Lanyang Basin (arsenic-exposed population)) **Population:** adult male residents of Taiwan from existing cohort n cases: 129 n control: 48	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentrations determined from well water samples collected during home interview **Population-Level Exposure:** 0.15-3,590 ppb range	**Outcome: erectile dysfunction (IIEF ≤ 21)** ***drinking water arsenic concentration, ppb*** Exp. Level / n / adjOR / (CI) ≤ 50 / NR / 1 / n/a >50 / NR / 3 / 1.0, 9.2 Stat Method: Multivariable logistic regression analysis **Outcome: severe erectile dysfunction (IIEF ≤ 7)** ***drinking water arsenic concentration, ppb*** Exp. Level / n / adjOR / (CI) ≤ 50 / NR / 1 / n/a >50 / NR / 7.5 / 1.8, 30.9 Stat Method: Multivariable logistic regression analysis
Hsieh et al. (2008b) **Study Type:** case-control (nested) **Location:** Taiwan (northeastern; Lanyang Basin of Ilan County) **Population:** adults and children genotyped for APOE and MCP-1 n cases: 235 n control: 244	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated based on arsenic concentration in well water and self-reported years of drinking well water during successive periods of living in different villages **Population-Level Exposure:** not available	**Outcome: carotid atherosclerosis** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) ≤ 0.2 / NR / 1 / n/a 0.3-1 / NR / 1.2 / 0.5, 2.6 ≥ 1.1 / NR / 1.7 / 0.9, 3.1 Stat Method: multiple logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic concentrations determined from well water samples collected during home interview	**Outcome: carotid atherosclerosis** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 10 / NR / 1 / n/a 10.1-50.0 / NR / 1.8 / 1.0, 3.2 ≥ 50.1 / NR / 1.9 / 1.1, 3.1 Stat Method: multiple logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
	Population-Level Exposure: 87.2 µg/L median, 43-182.2 µg/L 25th percentile	
Islam et al. (2012a) **Study Type:** cross-sectional **Location:** Bangladesh (Comilla, Jhenida districts) **Population:** adults living in unions of high arsenic contamination n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated by multiplying arsenic concentration of single tube well measurement for each individual with self-reported duration of use; subjects grouped for analysis above and below maximum acceptable limit in drinking water in Bangladesh (50 µg/L) and as quartiles **Population-Level Exposure:** 10-262 µg/L range	**Outcome: diastolic hypertension** ***cumulative drinking water arsenic exposure, µg/L*** Exp. Level / n / adjOR / (CI) <50 / 64 / 1 / n/a ≥ 50 / 50 / 1.24 / 0.76, 2.01 Stat Method: Multiple logistic regression, Cuzick's nonparametric test for trend **Outcome: increased pulse pressure** ***cumulative drinking water arsenic exposure, µg/L*** Exp. Level / n / adjOR / (CI) <50 / 15 / 1 / n/a ≥ 50 / 26 / 3.54 / 1.46, 8.57 Stat Method: Multiple logistic regression, Cuzick's nonparametric test for trend **Outcome: overall hypertension** ***cumulative drinking water arsenic exposure, µg/L*** Exp. Level / n / adjOR / (CI) <50 / 43 / 1 / n/a ≥ 50 / 23 / 0.93 / 0.49, 1.78 Stat Method: Multiple logistic regression, Cuzick's nonparametric test for trend ***cumulative drinking water arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) 10-22 / 22 / 1 / n/a 23-32 / 19 / 1.33 / 0.67, 2.62 33-261 / 13 / 1.1 / 0.49, 2.44 ≥ 262 / 12 / 0.96 / 0.42, 2.23 Stat Method: Multiple logistic regression, Cuzick's nonparametric test for trend **Outcome: pulse pressure** ***cumulative drinking water arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) 10-22 / 5 / 1 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		23-32 10 3.87 1.22, 12.20 33-261 10 4.32 1.23, 15.11 ≥ 262 16 7.32 2.18, 24.60 Stat Method: Multiple logistic regression, Cuzick's nonparametric test for trend
		Outcome: systolic hypertension
		cumulative drinking water arsenic exposure, µg/L Exp. Level / n / adjOR / (CI) <50 47 1 n/a ≥ 50 30 1.11 0.61, 2.02 Stat Method: Multiple logistic regression, Cuzick's nonparametric test for trend
Jensen and Hansen (1998) **Study Type:** cross-sectional **Location:** Denmark region not available **Population:** occupationally exposed adult workers n cases: 40 n control: 26	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration determined from two urine samples collected from each individual **Population-Level Exposure:** 12-80 nmol/mmol creatinine range	**Outcome: systolic blood pressure**
		urinary arsenic concentration by group, nmol/mmol creatinine Exp. Level / n / mean / (CI) unexposed NR 119.9 n/a colleagues of workers NR 122.8 n/a workers handling As directly NR 127.5 n/a Stat Method: Kruskal-Wallis test comparing mean values of systolic blood pressure
Jones et al. (2011) **Study Type:** cross-sectional **Location:** United States region not available **Population:** NHANES 2003-2008, adult participants with total arsenic assessed in urine	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from single sample for each individual; subjects grouped in quartiles for analysis **Population-Level Exposure:** 8.3 µg/L median, 4.2-17.1 µg/L 25th percentile	**Outcome: hypertension**
		dimethylarsinate concentration, µg/L Exp. Level / n / adjOR / (CI) per doubling of arsenic 1,761 1.11 0.99, 1.24 Stat Method: Logistic regression
		dimethylarsinate concentration (quartiles), µg/L Exp. Level / n / adjOR / (CI) <2.0 415 1 n/a 2.0-3.6 461 1.05 0.77, 1.42 >3.6-6.0 448 1.18 0.84, 1.66 >6.0 437 1.24 0.84, 1.83 Stat Method: Logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
n cases: 4,167 n control: n/a		***total urinary arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) per doubling of arsenic / 1,761 / 0.98 / 0.86, 1.11 Stat Method: Logistic regression ***total urinary arsenic concentration (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) <4.2 / 418 / 1 / n/a 4.2-8.3 / 451 / 1.08 / 0.83, 1.40 >8.3-17.1 / 446 / 1.3 / 0.94, 1.80 >17.1 / 446 / 1.17 / 0.75, 1.83 Stat Method: Logistic regression ***total urinary arsenic concentration minus arsenobetaine, µg/L*** Exp. Level / n / adjOR / (CI) per doubling of arsenic / 1,761 / 1.03 / 0.94, 1.14 Stat Method: Logistic regression ***total urinary arsenic concentration minus arsenobetaine (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) <3.1 / 426 / 1 / n/a 3.1-5.8 / 428 / 1.07 / 0.81, 1.40 >5.8-10.8 / 463 / 1.33 / 0.95, 1.85 >10.8 / 432 / 1.27 / 0.88, 1.83 Stat Method: Logistic regression
Karim et al. (2013) **Study Type:** cross-sectional **Location:** Bangladesh (North-west (Marua, Kestopur, Bheramara) and Chowkoli village) **Population:** Residents from arsenic-endemic and non-endemic areas	**Exposure Surrogate:** drinking water **Exposure Description:** water samples collected from tube wells used as primary drinking water source for study participants; no details provided on individual-level exposure characterization **Population-Level Exposure:** 1.06 µg/L mean 0.04SD	**Outcome: C-reactive protein (CRP)** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.139 / 0.084, 0.193 Stat Method: multivariate linear regression ***water arsenic concentration (tertiles), µg/L*** Exp. Level / n / mean / (CI) 0.03-13.17 (non-endemic) / NR / 0.78 / n/a 0.46-69.4 / NR / 1.15 / n/a 76-205 / NR / 1.75 / n/a 214-546 / NR / 2.82 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
of Bangladesh n cases: 218 n control: 106		Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: HDL** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.054 -0.068, -0.041 Stat Method: multivariate linear regression ***water arsenic concentration (tertiles), µg/L*** Exp. Level n mean (CI) 0.03-13.17 (non-endemic) NR 42.87 n/a 0.46-69.4 NR 32.1 n/a 76-205 NR 31.2 n/a 214-546 NR 29.4 n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: intercellular adhesion molecule-1 (ICAM-1)** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level n adjBeta (CI) continuous NR 0.042 0.029, 0.055 Stat Method: multivariate linear regression ***water arsenic concentration (tertiles), µg/L*** Exp. Level n mean (CI) 0.03-13.17 (non-endemic) NR 371.4 n/a 0.46-69.4 NR 518.1 n/a 76-205 NR 520.3 n/a 214-546 NR 549.2 n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: LDL** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.028 -0.045, -0.011

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multivariate linear regression ***water arsenic concentration (tertiles), µg/L*** Exp. Level / n / mean / (CI) 0.03-13.17 (non-endemic) / NR / 88.69 / n/a 0.46-69.4 / NR / 68.4 / n/a 76-205 / NR / 71.8 / n/a 214-546 / NR / 80.4 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: oxidized high density lipoprotein-low density lipoprotein (Ox-LDL/HDL)** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.058 / 0.044, 0.072 Stat Method: multivariate linear regression **Outcome: oxidized low density lipoprotein (Ox-LDL)** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.041 / 0.029, 0.053 Stat Method: multivariate linear regression ***water arsenic concentration (tertiles), µg/L*** Exp. Level / n / mean / (CI) 0.03-13.17 (non-endemic) / NR / 39.7 / n/a 0.46-69.4 / NR / 48.9 / n/a 76-205 / NR / 49 / n/a 214-546 / NR / 56.5 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: Total Cholesterol (TC)** ***water arsenic concentration (log-transformed), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.025 / -0.035, -0.015

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multivariate linear regression
		Outcome: vascular cell adhesion molecule-1 (VCAM-1)
		water arsenic concentration (log-transformed), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.036 / 0.023, 0.05 Stat Method: multivariate linear regression
		water arsenic concentration (tertiles), µg/L Exp. Level / n / mean / (CI) 0.03-13.17 (non-endemic) / NR / 420.3 / n/a 0.46-69.4 / NR / 589.7 / n/a 76-205 / NR / 604.1 / n/a 214-546 / NR / 623.7 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
	Exposure Surrogate: hair **Exposure Description:** hair samples collected for each study participant and washed **Population-Level Exposure:** 0.61 µg/g mean 0.12SD	**Outcome: C-reactive protein (CRP)**
		arsenic concentration in hair(log-transformed), µg/g Exp. Level / n / adjBeta / (CI) continuous / NR / 0.276 / 0.177, 0.374 Stat Method: multivariate linear regression
		arsenic concentration in hair (tertiles), µg/g Exp. Level / n / mean / (CI) 0.03-1.62 (non-endemic) / NR / 0.78 / n/a 0.25-2.37 / NR / 1.74 / n/a 2.45-4.95 / NR / 1.37 / n/a 5-37.24 / NR / 2.64 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
		Outcome: HDL
		arsenic concentration in hair(log-transformed), µg/g Exp. Level / n / adjBeta / (CI) continuous / NR / -0.085 / -0.11, -0.059 Stat Method: multivariate linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		arsenic concentration in hair (tertiles), µg/g Exp. Level / n / mean / (CI) 0.03-1.62 (non-endemic) / NR / 42.87 / n/a 0.25-2.37 / NR / 31.1 / n/a 2.45-4.95 / NR / 31.3 / n/a 5-37.24 / NR / 30.3 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
		Outcome: intercellular adhesion molecule-1 (ICAM-1)
		arsenic concentration in hair(log-transformed), µg/g Exp. Level / n / adjBeta / (CI) continuous / NR / 0.091 / 0.068, 0.114 Stat Method: multivariate linear regression
		arsenic concentration in hair (tertiles), µg/g Exp. Level / n / mean / (CI) 0.03-1.62 (non-endemic) / NR / 371.4 / n/a 0.25-2.37 / NR / 548.9 / n/a 2.45-4.95 / NR / 519.3 / n/a 5-37.24 / NR / 520.5 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
		Outcome: LDL
		arsenic concentration in hair(log-transformed), µg/g Exp. Level / n / adjBeta / (CI) continuous / NR / -0.04 / -0.078, -0.015 Stat Method: multivariate linear regression
		arsenic concentration in hair (tertiles), µg/g Exp. Level / n / mean / (CI) 0.03-1.62 (non-endemic) / NR / 88.69 / n/a 0.25-2.37 / NR / 70 / n/a 2.45-4.95 / NR / 70.2 / n/a 5-37.24 / NR / 80.5 / n/a Stat Method: One-Way ANOVA followed by

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Bonferroni multicomparison test. **Outcome: oxidized high density lipoprotein-low density lipoprotein (Ox-LDL/HDL)** ***arsenic concentration in hair(log-transformed), µg/g*** Exp. Level n adjBeta (CI) continuous NR 0.1 0.074, 0.127 Stat Method: multivariate linear regression **Outcome: oxidized low density lipoprotein (Ox-LDL)** ***arsenic concentration in hair(log-transformed), µg/g*** Exp. Level n adjBeta (CI) continuous NR 0.086 0.064, 0.108 Stat Method: multivariate linear regression ***arsenic concentration in hair (tertiles), µg/g*** Exp. Level n mean (CI) 0.03-1.62 (non-endemic) NR 39.7 n/a 0.25-2.37 NR 44.4 n/a 2.45-4.95 NR 50.3 n/a 5-37.24 NR 59.5 n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: Total Cholesterol (TC)** ***arsenic concentration in hair(log-transformed), µg/g*** Exp. Level n adjBeta (CI) continuous NR -0.038 -0.057, -0.02 Stat Method: multivariate linear regression ***arsenic concentration in hair (tertiles), µg/g*** Exp. Level n mean (CI) 0.03-1.62 (non-endemic) NR 147.3 n/a 0.25-2.37 NR 128.5 n/a 2.45-4.95 NR 122.6 n/a 5-37.24 NR 130.4 n/a Stat Method: One-Way ANOVA followed by

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Bonferroni multicomparison test
		Outcome: vascular cell adhesion molecule-1 (VCAM-1)
		arsenic concentration in hair(log-transformed), µg/g Exp. Level / n / adjBeta / (CI) continuous / NR / 0.086 / 0.062, 0.110 Stat Method: multivariate linear regression
		arsenic concentration in hair (tertiles), µg/g Exp. Level / n / mean / (CI) 0.03-1.62 (non-endemic) / NR / 420.3 / n/a 0.25-2.37 / NR / 605.1 / n/a 2.45-4.95 / NR / 588.4 / n/a 5-37.24 / NR / 624.2 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
	Exposure Surrogate: nail **Exposure Description:** nail samples collected from each individual and washed **Population-Level Exposure:** 6.65 µg/g mean	**Outcome: C-reactive protein (CRP)**
		arsenic concentration in nails (tertiles), µg/g Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) / NR / 0.78 / n/a 0.53-5.14 / NR / 1.39 / n/a 5.21-10.65 / NR / 1.99 / n/a 10.67-37.42 / NR / 2.33 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
		Outcome: HDL
		arsenic concentration in nails (tertiles), µg/g Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) / NR / 42.87 / n/a 0.53-5.14 / NR / 32.2 / n/a 5.21-10.65 / NR / 30.3 / n/a 10.67-37.42 / NR / 30.3 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
		Outcome: intercellular adhesion molecule-1

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		(ICAM-1) ***arsenic concentration in nails (tertiles), µg/g*** Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) / NR / 371.4 / n/a 0.53-5.14 / NR / 530.9 / n/a 5.21-10.65 / NR / 533.5 / n/a 10.67-37.42 / NR / 523.8 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: LDL** ***arsenic concentration in nails (tertiles), µg/g*** Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) / NR / 88.69 / n/a 0.53-5.14 / NR / 73.2 / n/a 5.21-10.65 / NR / 71.8 / n/a 10.67-37.42 / NR / 75.8 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: oxidized low density lipoprotein (Ox-LDL)** ***arsenic concentration in nails (tertiles), µg/g*** Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) / NR / 39.7 / n/a 0.53-5.14 / NR / 49.3 / n/a 5.21-10.65 / NR / 49.9 / n/a 10.67-37.42 / NR / 55.4 / n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: Total Cholesterol (TC)** ***arsenic concentration in nails (tertiles), µg/g*** Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) / NR / 147.3 / n/a 0.53-5.14 / NR / 126.6 / n/a 5.21-10.65 / NR / 125.8 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		10.67-37.42 NR 129 n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test. **Outcome: vascular cell adhesion molecule-1 (VCAM-1)** ***arsenic concentration in nails (tertiles), µg/g*** Exp. Level / n / mean / (CI) 0.15-8.13 (non-endemic) NR 420.3 n/a 0.53-5.14 NR 602.1 n/a 5.21-10.65 NR 627.3 n/a 10.67-37.42 NR 589.1 n/a Stat Method: One-Way ANOVA followed by Bonferroni multicomparison test.
Kim and Lee (2011) **Study Type:** cross-sectional **Location:** South Korea (national) **Population:** KNHANES IV 2008, adult participants n cases: 1,677 n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from single sample for each individual **Population-Level Exposure:** 118.4 µg/g-creatinine geo mean, 112.9-123.8 µg/g-creatinine 95% CI lower	**Outcome: blood pressure** ***log-transformed total urinary arsenic - comb sex, µg/g-creatinine*** Exp. Level / n / adjRR / (CI) hypertension - no NR 1 n/a hypertension - yes NR 1.07 0.982, 1.167 Stat Method: multiple regression ***log-transformed total urinary arsenic - female, µg/g-creatinine*** Exp. Level / n / adjRR / (CI) hypertension - no NR 1 n/a hypertension - yes NR 0.994 0.865, 1.144 Stat Method: multiple regression ***log-transformed total urinary arsenic - male, µg/g-creatinine*** Exp. Level / n / adjRR / (CI) hypertension - no NR 1 n/a hypertension - yes NR 1.132 1.004, 1.276 Stat Method: multiple regression
Kim et al. (2013)	**Exposure Surrogate:** urine	**Outcome: mean systolic blood pressure**

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: case-control (nested) **Location:** United States (Arizona) **Population:** longitudinal study participants who developed diabetes within 10 years of initial screening n cases: 150 n control: 150	**Exposure Description:** concentrations of arsenic (total and inorganic) and metabolites measured in stored urine samples obtained at the baseline examination; adjusted for urinary creatinine **Population-Level Exposure:** 21.1 µg/L median, 15.3-29.4 µg/L 25th percentile	***total arsenic concentration, µg/L*** systolic blood pressure similar in cases and controls
Kunrath et al. (2013) **Study Type:** cross-sectional **Location:** Romania (Arad County) **Population:** adult men with normal blood pressure and low-to-moderate arsenic exposure from drinking water n cases: 19 n control: 16	**Exposure Surrogate:** drinking water **Exposure Description:** individual exposure assessment conducted by collecting water samples from current main drinking water source for each participant; mean (SD) water inorganic As for unexposed and exposed: 1 (0.2) and 40.2 (30.4), respectively **Population-Level Exposure:** 0.1-240 µg/L range	**Outcome: anticipatory stress (DBP difference from baseline)** ***water arsenic exposure, µg/L*** Exp. Level / n / mean / (CI) unexposed / NR / 11.2 / n/a exposed / NR / 20 / n/a Stat Method: multivariate ANOVA **Outcome: anticipatory stress (SBP difference from baseline)** ***water arsenic exposure, µg/L*** arsenic not significantly associated with anticipatory stress **Outcome: blood pressure (anticipatory stress recovery)** ***water arsenic exposure, µg/L*** arsenic not significantly associated with blood pressure **Outcome: blood pressure (anticipatory stress)** ***water arsenic exposure, µg/L*** Exp. Level / n / adjOR / (CI) unexposed / NR / 1 / n/a exposed / NR / 6.3 / 1.11, 35.67 Stat Method: binary logistic regression **Outcome: blood pressure (cold stress)** ***water arsenic exposure, µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjOR / (CI) unexposed / NR / 1 / n/a exposed / NR / 4.67 / 1.11, 19.65 Stat Method: binary logistic regression
		Outcome: cold stress (DBP difference from baseline)
		water arsenic exposure, µg/L Exp. Level / n / mean / (CI) unexposed / NR / 23.2 / n/a exposed / NR / 34 / n/a Stat Method: multivariate ANOVA
		Outcome: cold stress (SBP difference from baseline)
		water arsenic exposure, µg/L Exp. Level / n / mean / (CI) unexposed / NR / 20.6 / n/a exposed / NR / 38.5 / n/a Stat Method: multivariate ANOVA
		Outcome: recovery from anticipatory stress (DBP difference from baseline)
		water arsenic exposure, µg/L Exp. Level / n / mean / (CI) unexposed / NR / 10.5 / n/a exposed / NR / 20.9 / n/a Stat Method: multivariate ANOVA
		Outcome: recovery from anticipatory stress (SBP difference from baseline)
		water arsenic exposure, µg/L arsenic not significantly associated with recovery from anticipatory stress
		Outcome: recovery from cold stress (DBP difference from baseline)
		water arsenic exposure, µg/L Exp. Level / n / mean / (CI) unexposed / NR / 10.3 / n/a exposed / NR / 19.6 / n/a Stat Method: multivariate ANOVA
		Outcome: recovery from cold stress (SBP difference from baseline)

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		water arsenic exposure, µg/L Exp. Level / n / mean / (CI) unexposed / NR / 1.7 / n/a exposed / NR / 16.8 / n/a Stat Method: multivariate ANOVA
Kwok et al. (2007) **Study Type:** cross-sectional **Location:** China (Inner Mongolia (Lin He, Hanggin Houqi, and Wu Yuan counties)) **Population:** women with pregnancy outcome 12/1/1996-12/31/1999 n cases: 2,808 n control: 5,982	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative drinking water arsenic exposure assessed retrospectively by matching subjects to well water measurements from five randomly selected families in each subvillage **Population-Level Exposure:** 0-100 µg/L range	**Outcome: diastolic blood pressure** ***cumulative drinking water arsenic exposure, µg/L*** Exp. Level / n / adjBeta / (CI) <LOD to 20 / NR / 1 / n/a 21 to 50 / NR / 2.11 / 1.38, 2.84 51 to 100 / NR / 2.74 / 1.55, 3.93 >100 / NR / 3.08 / 1.84, 4.31 Stat Method: Analysis of covariance **Outcome: systolic blood pressure** ***cumulative drinking water arsenic exposure, µg/L*** Exp. Level / n / adjBeta / (CI) <LOD to 20 / NR / 1 / n/a 21 to 50 / NR / 1.88 / 1.03, 2.73 51 to 100 / NR / 3.9 / 2.52, 5.29 >100 / NR / 6.83 / 5.39, 8.27 Stat Method: Analysis of covariance
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2,203 n total: 2,203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: all heart disease** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 1.03 / n/a 1,000-4,999 / NR / 0.8 / n/a ≥ 5,000 / NR / 61 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 0.87 / n/a 1,000-4,999 / NR / 0.78 / n/a ≥ 5,000 / NR / 0.74 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort **Outcome: all other heart disease** ***cumulative arsenic exposure, ppb-years***

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		SMR for all other heart disease unchanged from expected in males; SMR significantly increased in low exposure females only
		Outcome: aortic aneurysm
		cumulative arsenic exposure, ppb-years SMR for aortic aneurysm unchanged from expected in males and females
		Outcome: arteriosclerosis
		cumulative arsenic exposure, ppb-years SMR for arteriosclerosis unchanged from expected in males and females
		Outcome: cerebrovascular disease
		cumulative arsenic exposure (females), ppb-years Exp. Level / n / SMR / (CI) <1,000 / NR / 0.97 / n/a 1,000-4,999 / NR / 1.05 / n/a ≥ 5,000 / NR / 0.63 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort
		Outcome: disease of arteries and capillaries
		cumulative arsenic exposure, ppb-years SMR for disease of arteries and capillaries unchanged from expected in males and females
		Outcome: hypertension without heart disease
		cumulative arsenic exposure, ppb-years SMR for hypertension without heart disease unchanged from expected in males and females
		Outcome: hypertensive heart disease
		cumulative arsenic exposure, ppb-years SMR for hypertensive heart disease significantly increased in low exposure males and medium exposure females only
		Outcome: ischemic heart disease
		cumulative arsenic exposure (females), ppb-years Exp. Level / n / SMR / (CI) <1,000 / NR / 0.68 / n/a 1,000-4,999 / NR / 0.62 / n/a ≥ 5,000 / NR / 0.62 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		cumulative arsenic exposure (males), ppb-years Exp. Level / n / SMR / (CI) <1,000 / NR / 0.83 / n/a 1,000-4,999 / NR / 0.74 / n/a ≥ 5,000 / NR / 0.7 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort
Li et al. (2013a) **Study Type:** cross-sectional **Location:** China (Tuoketuo County, Inner Mongolia) **Population:** residents exposed to arsenic in drinking water n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration of each tube well measured and provided by local public health government; cumulative arsenic exposure (CAE) calculated for each subject as: concentration in tube well that subject used in his/her residential duration multiplied by duration of water consumption **Population-Level Exposure:** 0-760 µg/L range	**Outcome: hypertension** ***water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <10 / NR / NR / n/a 10-50 / NR / 1.417 / 0.767, 2.618 >50 / NR / 1.937 / 1.018, 3.687 Stat Method: multiple logistic regression
Li et al. (2009) **Study Type:** cross-sectional **Location:** Taiwan (southwestern) **Population:** adult residents of arseniasis-endemic area n cases: 142 n control: 345	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative drinking water arsenic exposure assessed using an index of cumulative arsenic exposure based on median arsenic level in village well water and years of living in a village (self-reported); current exposure assessed based on speciated urinary arsenic measurements (not used in association analyses) **Population-Level Exposure:** 0.01-15 mg/L - yr range	**Outcome: carotid artherosclerosis** ***cumulative drinking water arsenic exposure (tertiles), mg/L - yr*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-15.0 / NR / 2.2 / 0.95, 5.09 >15.0 / NR / 2.74 / 1.34, 5.60 Stat Method: Logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic concentration obtained from previous surveys, citations provided in study	**Outcome: carotid artherosclerosis** ***drinking water arsenic concentration (tertiles), ppb*** Exp. Level / n / adjOR / (CI) <1 / NR / 1 / n/a 1-700 / NR / 3.04 / 1.48, 6.24 >700 / NR / 1.99 / .90, 4.37

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
	Population-Level Exposure: 1-700 ppb range	Stat Method: Logistic regression
Li et al. (2013b) **Study Type:** cross-sectional **Location:** China (Shanyin county of Shanxi province) **Population:** residents of arsenic-contaminated areas n cases: 604 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure estimated based on concentration in tube wells in mg/L and recall of water consumption years by questionnaire **Population-Level Exposure:** 0-0.65 mg/L-yr range	**Outcome: blood pressure - hypertension** ***cumulative arsenic exposure, mg/L-yr*** Exp. Level / n / adjOR / (CI) without hypertension / NR / 1 / n/a hypertension / NR / 1.752 / 0.992, 3.096 Stat Method: multiple logistic regression ***cumulative arsenic exposure concentration in water (tertiles), mg/L-yr*** Exp. Level / n / adjOR / (CI) <0.10 / 29 / 1 / n/a 0.10-0.35 / 30 / 1.204 / 0.632, 2.292 >0.35 / 45 / 1.871 / 1.022, 3.424 Stat Method: multiple logistic regression
	Exposure Surrogate: urine **Exposure Description:** aliquot samples used for each assay; speciation based on hydride generation of volatile arsines; standard reference materials used; final adjustment by concentration of creatinine; total arsenic calculated as sum of inorganic arsenic, MMA, DMA; represented by species and by percentage **Population-Level Exposure:** 93.77-250.61 µg/g-creatinine range	**Outcome: blood pressure - hypertension** ***urinary inorganic arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <7.31 / 51 / 1 / n/a 7.31-33.68 / 54 / 1.301 / 0.772, 2.192 >33.68 / 63 / 1.591 / 0.963, 2.628 Stat Method: multiple logistic regression ***urinary total arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <93.77 / 45 / 1 / n/a 93.77-250.61 / 52 / 1.085 / 0.641, 1.837 >250.61 / 71 / 1.648 / 0.999, 2.721 Stat Method: multiple logistic regression
Liao et al. (2012) **Study Type:** cohort (prospective) **Location:** Taiwan (Homei, Fusin, and Hsinming villages in Putai Township)	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated from artesian well water measured in the 1960s and duration of water consumption; median concentration in endemic area was 0.78 ppm prior to intervention in the 1970s, after which concentration reduced to	**Outcome: cardiovascular disease mortality** ***cumulative drinking water arsenic exposure concentration, ppm-years*** Exp. Level / n / HR / (CI) <14.7 / NR / 1 / n/a >14.7 / NR / 1.89 / 0.50, 7.10 NR / NR / NR / n/a Stat Method: Cox proportional hazards analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Population: adult residents of previously arseniasis-endemic area from existing cohort still living in area in 2002 n exposed: 380 n reference: 296 n total: 676	<0.01ppm **Population-Level Exposure:** 0.78 ppm-years median	
Moon et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,575	**Exposure Surrogate:** urine **Exposure Description:** arsenic species concentrations were measured in urine; participants with arsenic species concentrations below the limit of detection (5.1% for inorganic arsenic, 0.8% for MMA, 0.03% for DMA, and 2.1% for arsenobetaine), levels imputed as LOD divided by square root of 2 and arsenate) and methylated arsenic species (DMA and MMA) as a biomarker to integrate inorganic arsenic exposure from multiple sources. **Population-Level Exposure:** 5.8-15.7 µg/g-creatinine range	**Outcome: cardiovascular disease - incidence** ***concentration of inorganic plus methylated arsenic species in urine (quartiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) <5.8 / 265 / 1 / n/a 5.8-9.7 / 297 / 1.11 / 0.93, 1.32 9.8-15.7 / 291 / 0.97 / 0.80, 1.17 >15.7 / 331 / 1.09 / 0.90, 1.33 Stat Method: Cox proportional hazards models **Outcome: cardiovascular disease - mortality** ***concentration of inorganic plus methylated arsenic species in urine (quartiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) <5.8 / 86 / 1 / n/a 5.8-9.7 / 95 / 1.02 / 0.75, 1.39 9.8-15.7 / 115 / 1.15 / 0.84, 1.58 >15.7 / 143 / 1.29 / 0.93, 1.79 Stat Method: Cox proportional hazards models **Outcome: coronary heart disease - incidence** ***concentration of inorganic plus methylated arsenic species in urine (quartiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) <5.8 / 202 / 1 / n/a 5.8-9.7 / 206 / 1.03 / 0.84, 1.26 9.8-15.7 / 197 / 0.88 / 0.70, 1.10 >15.7 / 241 / 1.08 / 0.86, 1.35 Stat Method: Cox proportional hazards

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		models **Outcome: coronary heart disease - mortality** ***concentration of inorganic plus methylated arsenic species in urine (quartiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) <5.8 / 68 / 1 / n/a 5.8-9.7 / 67 / 0.89 / 0.62, 1.27 9.8-15.7 / 87 / 1.06 / 0.74, 1.53 >15.7 / 119 / 1.33 / 0.92, 1.93 Stat Method: Cox proportional hazards models **Outcome: stroke - incidence** ***concentration of inorganic plus methylated arsenic species in urine (quartiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) <5.8 / 55 / 1 / n/a 5.8-9.7 / 75 / 1.09 / 0.76, 1.57 9.8-15.7 / 62 / 1.07 / 0.72, 1.60 >15.7 / 72 / 1.18 / 0.77, 1.79 Stat Method: Cox proportional hazards models **Outcome: stroke - mortality** ***concentration of inorganic plus methylated arsenic species in urine (quartiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) <5.8 / 6 / 1 / n/a 5.8-9.7 / 17 / 1.3 / 0.50, 3.39 9.8-15.7 / 13 / 1.97 / 0.70, 5.55 >15.7 / 18 / 2.35 / 0.83, 6.69 Stat Method: Cox proportional hazards models
Mordukhovich et al. (2009) **Study Type:** cross-sectional	**Exposure Surrogate:** toenails **Exposure Description:** toenail samples from all 10 toes collected; samples were cleaned to remove contaminants and then sonicated; samples digested with	**Outcome: change in heart rate-corrected QT interval duration (milliseconds)** ***toenail arsenic concentration, µg/g*** Exp. Level / n / change / (CI) per 0.059-µg/g (IQR) increase / NR / 2.5 / 0.11, 4.9

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Location: United States (MA) **Population:** elderly men from Veterans Administration Normative Aging Study n cases: n/a n control: n/a	nitric acid and diluted with deionized water **Population-Level Exposure:** 0.069 µg/g median, 0.052-0.11 µg/g 25th percentile	Stat Method: multivariate linear regression **Outcome: change in QT interval duration (milliseconds)** ***toenail arsenic concentration, µg/g*** Exp. Level / n / change / (CI) per 0.059-µg/g (IQR) increase / NR / 3.8 / 0.82, 6.8 Stat Method: multivariate linear regression
Mumford et al. (2007) **Study Type:** cross-sectional **Location:** China (Ba Men) **Population:** residents of high, medium, and low exposure areas for arsenic in drinking water n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** samples collected from study subject's homes **Population-Level Exposure:** 0.1-690 µg/L range	**Outcome: heart rate** ***well water arsenic concentration, µg/L*** individuals with prolonged QTc demonstrated statistical significant increase in heart rate in medium- (p=0.0194) and high-exposure (p=0.0018) groups (t-test) **Outcome: QT interval** ***well water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <LOD-21 / NR / 1 / n/a 100-300 / NR / 3.829 / 1.128, 12.993 430-690 / NR / 8.848 / 2.723, 28.748 Stat Method: binary logistic regression
Osorio-Yáñez et al. (2013) **Study Type:** cross-sectional **Location:** Mexico (Zimapan region) **Population:** children exposed to environmental inorganic arsenic n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** spot urine samples were collected; reference standards were used to validate low and high concentrations of arsenic in urine **Population-Level Exposure:** 74.31 ng/mL mean 57.04SD	**Outcome: cartoid intimamedia thickness (cIMT)** ***total arsenic concentration in urine, ng/mL*** Exp. Level / n / adjBeta / (CI) <35 ng/mL / NR / NR / n/a 35-70 ng/mL / NR / 0.035 / -0.0028, 0.072 >70 ng/mL / NR / 0.058 / 0.0198, 0.095 Stat Method: robust multivariable linear regression analysis
Rahman et al. (1999a)	**Exposure Surrogate:** drinking water	**Outcome: hypertension**

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cohort (retrospective) **Location:** Bangladesh (Faridpur, Nawabgong, Jessore, and Narayongong districts) **Population:** adults residents of village with history of higher than average arsenic in drinking water based on existing surveys n exposed: 1,481 n reference: 114 n total: 1,595	**Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of use **Population-Level Exposure:** 0-10 mg-Y/L	***cumulative drinking water arsenic exposure, mg-Y/L*** Exp. Level / n / PR (M-H) / (CI) 0 / 9 / 1 / n/a <1.0 / 13 / 0.8 / 0.3, 1.7 1.0-5.0 / 83 / 1.5 / 0.7, 2.9 >5.0-10.0 / 40 / 2.2 / 1.1, 4.4 >10.0 / 62 / 3 / 1.5, 5.8 Stat Method: Linear regression model
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic concentrations calculated as time-weighted average based on levels obtained from existing reports **Population-Level Exposure:** 0-1 mg/L range	**Outcome: hypertension** ***drinking water arsenic concentration, mg/L*** Exp. Level / n / PR (M-H) / (CI) 0 / 9 / 1 / n/a <0.5 / 50 / 1.2 / 0.6, 2.3 0.5 to 1.0 / 93 / 2.2 / 1.1, 4.3 >1.0 / 55 / 2.5 / 1.2, 4.9 Stat Method: Linear regression model
Sohel et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** Health and Demographic Surveillance System 1991-2000, adults and children with nonaccidental deaths 1991-2000 n exposed: 93,415 n total: 93,415	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative drinking water arsenic concentration based on current arsenic concentrations (reasonably stable over time); average household exposure (used as proxy for individual exposure) calculated for each calendar year from 1970, based on information obtained from the current population present in that specific household for each year **Population-Level Exposure:** 10-300 µg/L range	**Outcome: cardiovascular disease deaths** ***cumulative water arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <10 / 129 / 1 / n/a 10-49 / 153 / 1.03 / 0.82, 1.29 50-149 / 476 / 1.16 / .96, 1.40 150-299 / 388 / 1.23 / 1.01, 1.51 ≥ 300 / 152 / 1.37 / 1.07, 1.77 Stat Method: Cox proportional hazard model
Tseng et al. (1996) **Study Type:** cross-sectional	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-	**Outcome: peripheral vascular disease** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / NR / 1 / n/a 0.1-19.9 / NR / 2.77 / 0.84, 9.14

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Location: Taiwan (Homei, Fuhsin, and Hsinming villages in Putai Township) **Population:** adults living in blackfoot disease-endemic township n cases: 582 n control: n/a	reported years of drinking well water during successive periods of living in different villages **Population-Level Exposure:** 0-20 mg/L - yr range	≥ 20.0 NR 4.28 1.26, 14.54 Unknown NR 1.63 0.50, 5.33 Stat Method: Multivariate logistic regression
Tseng et al. (1997) **Study Type:** cross-sectional **Location:** Taiwan (Homei, Fuhsin, and Hsinming villages in Putai Township) **Population:** adults living in blackfoot disease-endemic township n cases: 533 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of drinking well water during successive periods of living in different villages **Population-Level Exposure:** 0-20 mg/L - yr range	**Outcome: peripheral vascular disease** ***cumulative drinking water arsenic exposure, ABI >1.2 excluded, mg/L - yr*** Exp. Level n adjOR (CI) 0 NR 1 n/a 0.1-19.9 NR 3.01 0.84, 10.75 ≥ 20 NR 5.6 1.50, 20.92 Unknown NR 1.58 0.46, 5.37 Stat Method: Multivariate logistic regression
Tseng et al. (2003) **Study Type:** cross-sectional **Location:** Taiwan (Homei, Fuhsin, and Hsinming villages in Putai Township) **Population:** adults living in blackfoot disease-endemic township n cases: 462	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of drinking well water during successive periods of living in different villages **Population-Level Exposure:** 0-15 mg/L - yr range	**Outcome: ischemic heart disease** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level n adjOR (CI) 0 NR 1 n/a 0.1-14.9 NR 1.6 0.48, 5.34 ≥ 15 NR 3.6 1.11, 11.65 Stat Method: Multivariate logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
n control: n/a		
Wade et al. (2009) **Study Type:** cohort (retrospective) **Location:** China (Shahai village, Inner Mongolia) **Population:** decreased male and female adults and children living in village history of higher than average arsenic in drinking water n exposed: 562 n total: 572	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic exposure calculated from single well water sample collected from each household; results below LOD assigned one-half of LOD **Population-Level Exposure:** 38 µg/L mean	**Outcome: heart disease mortality** ***drinking water arsenic concentration (exposed since before 1990), µg/L*** Exp. Level / n / IRR / (CI) 0-5 / 36 / 1 / n/a 5.1-20 / 12 / 0.75 / 0.37, 1.51 20.1-100 / 37 / 1.28 / 0.79, 2.07 100.1-300 / 15 / 1.6 / 0.87, 2.95 >300 / 2 / 5.08 / 1.45, 17.81 Stat Method: multivariate Poisson regression model ***drinking water arsenic concentration (exposed since before 1995), µg/L*** Exp. Level / n / IRR / (CI) 0-5 / 44 / 1 / n/a 5.1-20 / 26 / 1.07 / 0.64, 1.78 20.1-100 / 72 / 1.22 / 0.82, 1.82 100.1-300 / 17 / 1.55 / 0.88, 2.73 >300 / 2 / 2.47 / 0.50, 12.18 Stat Method: multivariate Poisson regression model ***drinking water arsenic concentration (per 50 µg/L increase), µg/L*** Exp. Level / n / IRR / (CI) 50 µg/L increase / NR / 1.12 / 1.01, 1.23 Stat Method: multivariate Poisson regression model **Outcome: stroke mortality** ***drinking water arsenic concentration (exposed since before 1990), µg/L*** Exp. Level / n / IRR / (CI) 0-5 / 40 / 1 / n/a 5.1-20 / 13 / 0.62 / 0.33, 1.18 20.1-100 / 20 / 0.65 / 0.38, 1.12 100.1-300 / 6 / 0.58 / 0.26, 1.29 >300 / 1 / 1.64 / 0.31, 8.77 Stat Method: multivariate Poisson regression model ***drinking water arsenic concentration (exposed since before 1995), µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / IRR / (CI) 0-5 / 53 / 1 / n/a 5.1-20 / 16 / 0.47 / 0.27, 0.84 20.1-100 / 41 / 0.51 / 0.34, 0.79 100.1-300 / 7 / 0.52 / 0.25, 1.10 >300 / 1 / 1.02 / 0.16, 6.71 Stat Method: multivariate Poisson regression model
		drinking water arsenic concentration (per 50 µg/L increase), µg/L Exp. Level / n / IRR / (CI) 50 µg/L increase / NR / 0.82 / 0.65, 1.03 Stat Method: multivariate Poisson regression model
Wang et al. (2002) **Study Type:** cohort (prospective) **Location:** Taiwan (southwestern; Homei, Fushin, and Hsinming villages in Putai Township) **Population:** adults living in arseniasis-endemic township n exposed: 436 n total: 436	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of drinking well water during successive periods of living in different villages; arsenic levels in well water collected in previous studies conducted in the 1960s **Population-Level Exposure:** 0-20 mg/L - yr range	**Outcome: IMT ≥ 1.0mm** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / NR / 1 / n/a 0.1-19.9 / NR / 1.9 / 0.9, 4.1 ≥ 20 / NR / 2.9 / 1.2, 6.9 Stat Method: multiple logistic regression (multivariate) analysis
		Outcome: presence of plaque ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / NR / 1 / n/a 0.1-19.9 / NR / 1.2 / 0.4, 3.4 ≥ 20 / NR / 2.3 / 0.8, 6.4 Stat Method: multiple logistic regression (multivariate) analysis
		Outcome: presence of plaque or IMT ≥ 1.0mm ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / NR / 1 / n/a 0.1-19.9 / NR / 1.8 / 0.8, 3.8 ≥ 20 / NR / 3.1 / 1.3, 7.4 Stat Method: multiple logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		(multivariate) analysis
Wang et al. (2009a) **Study Type:** cross-sectional **Location:** Taiwan (Homei, Fuhsin, Hsingming villages in Putai township) **Population:** adults living in arseniasis-endemic townships n cases: 441 n control: 194	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime cumulative arsenic exposure calculated by multiplying the median arsenic level in specific village by duration of consumption of artesian well water in that village; residential history used to sum products of concentration and consumption for the entire period when living in arseniasis-endemic area **Population-Level Exposure:** 0-20 mg/L - yr range	**Outcome: IMT (mm)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 0.84 / n/a 0.1-19.9 / NR / 1.13 / n/a ≥ 20 / NR / 1.49 / n/a Stat Method: Adjusted P for trend **Outcome: P wave (ms)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 93.2 / n/a 0.1-19.9 / NR / 92.9 / n/a ≥ 20 / NR / 91.7 / n/a Stat Method: Adjusted P for trend **Outcome: PR interval (ms)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 178.9 / n/a 0.1-19.9 / NR / 180.1 / n/a ≥ 20 / NR / 79.2 / n/a Stat Method: Adjusted P for trend **Outcome: Prevalence of carotid plaque (%)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 16.8 / n/a 0.1-19.9 / NR / 33.4 / n/a ≥ 20 / NR / 64.5 / n/a Stat Method: Adjusted P for trend **Outcome: Prevalence of IHD (%)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 5.8 / n/a 0.1-19.9 / NR / 11.7 / n/a ≥ 20 / NR / 25.1 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: Adjusted P for trend **Outcome: Prevalence of QTc-Fridericia >460 ms (%)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 8.5 / n/a 0.1-19.9 / NR / 20.6 / n/a ≥ 20 / NR / 54.1 / n/a Stat Method: Adjusted P for trend **Outcome: QRS duration (ms)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 87.9 / n/a 0.1-19.9 / NR / 86.9 / n/a ≥ 20 / NR / 86.7 / n/a Stat Method: Adjusted P for trend **Outcome: QT (ms)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 415.3 / n/a 0.1-19.9 / NR / 435.5 / n/a ≥ 20 / NR / 462.4 / n/a Stat Method: Adjusted P for trend **Outcome: QTc-Bazett (ms)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 416 / n/a 0.1-19.9 / NR / 436.8 / n/a ≥ 20 / NR / 464.7 / n/a Stat Method: Adjusted P for trend **Outcome: QTc-Fridericia (ms)** ***cumulative drinking water arsenic exposure, mg/L - yr*** Exp. Level / n / mean / (CI) ~0 / NR / 417.2 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
		0.1-19.9 NR 437.9 n/a ≥ 20 NR 469.7 n/a Stat Method: Adjusted P for trend
		Outcome: QTc-Fridericia prolongation
		cumulative drinking water arsenic exposure, mg/L - yr Exp. Level / n / adjOR / (CI) ~0 NR 1 n/a 0.1-19.9 NR 2.3 1.0, 5.3 ≥ 20 NR 7.6 3.1, 18.6 Stat Method: Multiple logistic regression analysis
Wang et al. (2011a) **Study Type:** cohort (prospective) **Location:** Taiwan (Homei, Fuhsin, and Hsinming villages in Putai Township) **Population:** adults living in arseniasis-endemic townships n exposed: 352 n total: 352	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative drinking water arsenic levels were calculated based on arsenic concentration in well water (median of wells within walking distance) and self-reported years of drinking well water during successive periods of living in different villages **Population-Level Exposure:** 930 mg/L - yr median, 5.6-15.6 mg/L - yr range	**Outcome: hypertension** ***cumulative drinking water arsenic exposure (tertiles), mg/L - yr*** Exp. Level / n / adjRR / (CI) <5.6 NR 1 n/a 5.6-15.6 NR 1.15 0.55, 2.40 >15.6 NR 1.18 0.50, 2.77 Stat Method: Logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic concentrations determined using median of wells within walking distance and self-reported information on residential history; arsenic levels in well water collected in previous studies conducted in the 1960s **Population-Level Exposure:** 930 µg/L median	**Outcome: hypertension** ***drinking water arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjRR / (CI) <538 NR 1 n/a 538-700 NR 1.18 0.60, 2.34 >700 NR 0.83 0.40, 1.74 Stat Method: Logistic regression
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic	**Outcome: hypertension** ***speciated urinary arsenic concentration (As[V]; tertiles), µg/g-creatinine*** Exp. Level / n / adjRR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
	species (As[V]) measured from sample (collected 2002-2003) for each individual **Population-Level Exposure:** 1.2-2.67 µg/g-creatinine range	<1.20 NR 1 n/a 1.20-2.67 NR 1.38 0.57, 3.34 >2.67 NR 2.43 1.01, 5.86 Stat Method: Logistic regression
Wu et al. (2006) **Study Type:** case-control **Location:** Taiwan (Lanyang Basin of Ilan County, northeastern Taiwan) **Population:** adults living in arseniasis-endemic township, health examinations 1997-1998 n cases: 163 n control: 163	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of use **Population-Level Exposure:** 1.7-4.21 µg/L-year range	**Outcome: carotid atherosclerosis** ***cumulative drinking water arsenic exposure (tertiles), µg/L-year*** Exp. Level n adjOR (CI) ≤ 1.70 NR 1 n/a 1.71 - 4.20 NR 1.7 0.9, 3.2 ≥ 4.21 NR 2.9 1.6, 5.3 Trend across tertiles NR 1.7 1.3, 2.3 Stat Method: Linear regression analysis
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic exposure calculated from single well water sample collected from each household **Population-Level Exposure:** 50-100.01 µg/L range	**Outcome: carotid atherosclerosis** ***drinking water arsenic concentration (tertiles), µg/L*** Exp. Level n adjOR (CI) ≤ 50.00 NR 1 n/a 50.01 - 100.00 NR 1.9 0.9, 3.8 ≥ 100.01 NR 2.6 1.3, 5.0 Trend across tertiles NR 1.6 1.1, 2.1 Stat Method: Linear regression analysis; logistic regression
Wu et al. (2010) **Study Type:** case-control (nested) **Location:** Taiwan (Lanyang Basin) **Population:** adults living in arseniasis-endemic township, health examinations 1998-1999 n cases: 250 n control: 256	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic exposure calculated from single well water sample collected from each household **Population-Level Exposure:** 10-300 µg/L range	**Outcome: carotid atherosclerosis** ***average drinking water arsenic exposure, µg/L*** Exp. Level n adjOR (CI) ≤ 10 NR 1 n/a 10.1-50 NR 2.58 0.70, 9.56 50.1-100 NR 2.98 1.21, 7.34 100.1-300 NR 3.07 1.23, 7.65 >300 NR 2.62 1.04, 6.60 Stat Method: logistic regression analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Cardiovascular Disease		
Reference and Study Design	**Exposure Measures**	**Results**
Xia et al. (2009) **Study Type:** cross-sectional **Location:** China (Bayingnormen, Shahai village) **Population:** adults and children living in arseniasis-endemic village n cases: 11,416 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration in drinking water; exposure calculated from single well water sample collected from each household **Population-Level Exposure:** 37.94 µg/L mean	**Outcome: cardiovascular disease** ***drinking water arsenic concentration (per 50 µg/L increase) by sex, µg/L*** Exp. Level / n / adjOR / (CI) continuous (males) / NR / 1.1 / n/a continuous (females) / NR / 0.99 / n/a Stat Method: logistic regression model **Outcome: stroke** ***drinking water arsenic concentration (per 50 µg/L increase) by sex, µg/L*** Exp. Level / n / adjOR / (CI) continuous (males and females) / NR / 1.03 / n/a Stat Method: logistic regression model

--: not reported; n: number of cases (when presented in Results column)

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5.3 Summary of Observational Epidemiology Studies for Health Effect Category: Clinical Chemistry and Urinalysis

Summary of Observational Epidemiology Studies for Health Effect Category: Clinical Chemistry and Urinalysis		
Reference and Study Design	**Exposure Measures**	**Results**
Casale et al. (2013) **Study Type:** cross-sectional **Location:** Italy (Central Italy) **Population:** municipal policemen and police drivers n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** spot urine samples collected from each worker at the end of the work shift for 4 working days in succession **Population-Level Exposure:** 2.6-54.7 µg/g-creatinine range	**Outcome: ALT/GPT** ***log total urinary arsenic concentration, µg/g-creatinine*** Exp. Level: continuous; n: NR; adjBeta: 0.374; (CI): n/a Stat Method: multiple linear regression **Outcome: AST/GOT** ***log total urinary arsenic concentration, µg/g-creatinine*** arsenic not significantly associated with AT/GOT **Outcome: γ-GT (GGT)** ***log total urinary arsenic concentration, µg/g-creatinine*** arsenic not significantly associated with γ-GT
Chen et al. (2011c) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** HEALS n total: 10,957	**Exposure Surrogate:** drinking water **Exposure Description:** water samples from all 5,966 wells in the area were tested at baseline; samples below LOD reanalyzed using ICP-MS with a detection limit of 0.1 µg/L **Population-Level Exposure:** 0.1-864 µg/L range	**Outcome: proteinuria** ***baseline well arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI): 0.1-7 / NR / 1 / n/a 8-39 / NR / 1.01 / 0.77, 1.27 40-91 / NR / 1.33 / 0.97, 1.57 92-179 / NR / 1.54 / 1.18, 1.89 180-864 / NR / 1.65 / 1.26, 2 Stat Method: unconditional logistic regression
	Exposure Surrogate: urine **Exposure Description:** total arsenic levels were measured on spot urine samples obtained at baseline and at each follow-up visit (every 2 years) **Population-Level Exposure:**	**Outcome: proteinuria** ***change in urinary arsenic concentration since last visit, µg/L*** Exp. Level / n / HR / (CI): <-70 / NR / 0.84 / 0.67, 1.04 -70 to -17 / NR / 0.91 / 0.74, 1.12 -16 to 15 / NR / 1 / n/a 16 to 68 / NR / 1.17 / 0.97, 1.42 ≥ 69 / NR / 1.43 / 1.17, 1.74

Summary of Observational Epidemiology Studies for Health Effect Category: Clinical Chemistry and Urinalysis		
Reference and Study Design	**Exposure Measures**	**Results**
	1-206 µg/L range	Stat Method: Cox proportional hazard models ***baseline urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.48 / 1.12, 1.96 67-114 / NR / 1.65 / 1.25, 2.16 115-205 / NR / 1.53 / 1.16, 2.02 ≥ 206 / NR / 1.65 / 1.24, 2.20 Stat Method: unconditional logistic regression
Kim et al. (2013) **Study Type:** case-control (nested) **Location:** United States (Arizona) **Population:** longitudinal study participants who developed diabetes within 10 years of initial screening n cases: 150 n control: 150	**Exposure Surrogate:** urine **Exposure Description:** concentrations of arsenic (total and inorganic) and metabolites measured in stored urine samples obtained at the baseline examination; adjusted for urinary creatinine **Population-Level Exposure:** 21.1 µg/L median, 15.3-29.4 µg/L 25th percentile	**Outcome: mean albumin:creatinine ratio** ***total arsenic concentration, µg/L*** albumin:creatinine ratio similar in cases and controls

--: not reported; n: number of cases (when presented in Results column)

5.3.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Clinical Chemistry and Urinalysis

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5.4 Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Calderon et al. (2001) **Study Type:** cross-sectional **Location:** Mexico (San Luis Potosi) **Population:** children attending Morales elementary school 1.5 km from smelter and comparison group attending Martinez school 7 km away n cases: 41 n control: 39	**Exposure Surrogate:** urine **Exposure Description:** first morning void samples collected; standardized to urinary creatinine; log-transformed; recovery 98 +/- 4% **Population-Level Exposure:** 40.28-62.91 µg/g-creatinine range	**Outcome: concepts (similarities, comprehension, vocabulary)** ***mean urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / -0.12 / n/a 62.91 (Morales) / NR / -0.31 / n/a Stat Method: partial correlation coefficient calculation **Outcome: IQ (full)** ***mean urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / 0.04 / n/a 62.91 (Morales) / NR / -0.33 / n/a Stat Method: partial correlation coefficient calculation **Outcome: IQ (performance)** ***mean urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / 0.22 / n/a 62.91 (Morales) / NR / -0.24 / n/a Stat Method: partial correlation coefficient

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		calculation **Outcome: IQ (verbal)** ***mean urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / -0.24 / n/a 62.91 (Morales) / NR / -0.43 / n/a Stat Method: partial correlation coefficient calculation **Outcome: knowledge (vocabulary, information, arithmetic)** ***mean urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / -0.17 / n/a 62.91 (Morales) / NR / -0.41 / n/a Stat Method: partial correlation coefficient calculation **Outcome: sequential (arithmetic, digit span, coding)** ***mean urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / 0.2 / n/a 62.91 (Morales) / NR / -0.31 / n/a Stat Method: partial correlation coefficient calculation **Outcome: spatial (object assembly, block design, picture completion)** ***mean urinary arsenic concentration, µg/g-creatinine***

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / corr coeff / (CI) 40.28 (Martinez) / NR / 0.01 / n/a 62.91 (Morales) / NR / -0.22 / n/a Stat Method: partial correlation coefficient calculation
Gardner et al. (2013) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** children in Maternal and Infant Nutrition Interventions in Matlab (MINIMat) cohort	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration, samples collected from 1.5- and 5-year-old children **Population-Level Exposure:** 35-84 µg/L range	**Outcome: height** ***urinary arsenic exposure, µg/L*** Exp. Level / n / adjusted AR / (CI) low (≤ 5th percentile) / NR / 0 / n/a high (≥ 95th percentile) / NR / -0.5 / -1.2, 0.21 Stat Method: linear regression model
		Outcome: height-for-age z-score ***urinary arsenic exposure, µg/L*** inverse association with concurrent exposure to cadmium and arsenic
		Outcome: peak height velocity ***urinary arsenic exposure, µg/L*** inverse association with concurrent exposure to cadmium and arsenic
		Outcome: peak weight velocity ***urinary arsenic exposure, µg/L*** inverse association with concurrent exposure to cadmium and arsenic
		Outcome: weight ***urinary arsenic exposure, µg/L*** Exp. Level / n / adjusted AR / (CI) low (≤ 5th percentile) / NR / 0 / n/a high (≥ 95th percentile) / NR / -0.33 / -0.60, -0.06 Stat Method: linear regression model
		Outcome: weight-for-age z-score

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		urinary arsenic exposure, µg/L inverse association with concurrent exposure to cadmium and arsenic
Guan et al. (2012) **Study Type:** cross-sectional **Location:** China (Dalian) **Population:** 125 pairs of mothers and their infants with prenatal exposure to arsenic n cases: n/a n control: n/a	**Exposure Surrogate:** blood **Exposure Description:** arsenic concentrations in maternal cubital vein blood and infant umbilical cord vein blood collected immediately after admission (mother) and after clamping and before delivery of the placenta (infant); mean values of maternal and cord blood arsenic concentrations: 6.91 and 5.41 µg/L, respectively; median values: 5.30 and 3.71 µg/L, respectively **Population-Level Exposure:** mean maternal blood: 6.91 µg/l; mean cord blood: 5.41 µg/l	**Outcome: birth height** ***maternal arsenic blood concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.1 n/a Stat Method: multiple linear regression **Outcome: birth weight** ***maternal arsenic blood concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.02 n/a Stat Method: multiple linear regression **Outcome: chest circumference** ***maternal arsenic blood concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.1 n/a Stat Method: multiple linear regression **Outcome: head circumference** ***fetal arsenic cord blood concentrations, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.06 n/a Stat Method: multiple linear regression
Hamadani et al. (2010) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** Children of pregnant women from a MINIMat trial cohort in Matlab, Bangladesh n total: 1,745	**Exposure Surrogate:** urine **Exposure Description:** child's urine collected at 18 months and analyzed for arsenic and metabolites MMA and DMA; concentrations adjusted by specific gravity (1.009 g/ml) **Population-Level Exposure:** 35 µg/L median, 18.2-80.8 µg/L 25th percentile	**Outcome: language comprehension** ***children's urinary arsenic concentration, µg/L*** Exp. Level n regr coeff (CI) continuous NR 0.25 -0.6, 1 Stat Method: multiple linear regression analysis **Outcome: language expression** ***children's urinary arsenic concentration, µg/L*** Exp. Level n regr coeff (CI) continuous NR -0.001 -0.03, 0.03 Stat Method: multiple linear regression analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: mental development index
		children's urinary arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 0.3 -0.9, 1.5 Stat Method: multiple linear regression analysis
		Outcome: psychomotor development index
		children's urinary arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR -0.07 -1.5, 1.3 Stat Method: multiple linear regression analysis
	Exposure Surrogate: urine **Exposure Description:** maternal urine collected at gestation weeks 8 and 30 and analyzed for total arsenic; mean of 8- and 30-week concentrations used to represent exposure; concentrations adjusted by specific gravity (1.012 g/ml) **Population-Level Exposure:** 94.4 µg/L median, 45-216 µg/L 25th percentile	**Outcome: language comprehension**
		maternal urinary arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR -0.3 -1.3, 0.6 Stat Method: multiple linear regression analysis
		Outcome: language expression
		maternal urinary arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR -0.009 -0.04, 0.02 Stat Method: multiple linear regression analysis
		Outcome: mental development index
		maternal urinary arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 0.5 -0.9, 1.8 Stat Method: multiple linear regression analysis
		Outcome: psychomotor development index
		maternal urinary arsenic concentration, µg/L Exp. Level n regr (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		coeff continuous NR 0.3 -1.3, 1.9 Stat Method: multiple linear regression analysis
Hamadani et al. (2011) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** children in Maternal and Infant Nutrition Interventions in Matlab (MINIMat) cohort n total: 2,260	**Exposure Surrogate:** maternal urine **Exposure Description:** urinary arsenic levels measured gestational weeks 8 and 30 and characterized into quartiles **Population-Level Exposure:** 80 µg/L median, 25-400 µg/L 10th percentile	**Outcome: full scale IQ (FSIQ) score** ***maternal urinary arsenic concentration (gestation week 30) (quartiles), µg/L*** Exp. Level n mean (CI) 0-40 NR 76.7 n/a 41-82 NR 75.6 n/a 83-228 NR 74.4 n/a >228 NR 73.9 n/a Stat Method: ANOVA
		maternal urinary arsenic concentration (gestation week 8) (quartiles), µg/L Exp. Level n mean (CI) 0-36 NR 76.6 n/a 37-39 NR 75.9 n/a 80-206 NR 74.2 n/a >206 NR 74.2 n/a Stat Method: ANOVA
		log10 maternal urinary arsenic concentration (gestation week 30; females), µg/L Exp. Level n adjBeta (CI) continuous NR -1.3 -2.4, -0.3 Stat Method: linear regression
		log10 maternal urinary arsenic concentration (gestation week 30; males), µg/L Exp. Level n adjBeta (CI) continuous NR 0.1 -0.9, 1.1 Stat Method: linear regression
		log10 maternal urinary arsenic concentration (gestation week 8; females), µg/L Exp. Level n adjBeta (CI) continuous NR -0.9 -2.0, -0.2 Stat Method: linear regression
		log10 maternal urinary arsenic concentration (gestation week 8; males), µg/L Exp. Level n adjBeta (CI) continuous NR -0.2 -1.2, 0.9

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: linear regression
		Outcome: performance intelligence quotient (PIQ)
		maternal urinary arsenic concentration (gestation week 30) (quartiles), µg/L Exp. Level / n / mean / (CI) 0-40 / NR / 77.3 / n/a 41-82 / NR / 76.6 / n/a 83-228 / NR / 76 / n/a >228 / NR / 75.2 / n/a Stat Method: ANOVA
		maternal urinary arsenic concentration (gestation week 8) (quartiles), µg/L Exp. Level / n / mean / (CI) 0-36 / NR / 77.6 / n/a 37-39 / NR / 76.1 / n/a 80-206 / NR / 75.2 / n/a >206 / NR / 76 / n/a Stat Method: ANOVA
		Outcome: verbal IQ (VIQ) score
		maternal urinary arsenic concentration (gestation week 30) (quartiles), µg/L Exp. Level / n / mean / (CI) 0-40 / NR / 81.5 / n/a 41-82 / NR / 80.2 / n/a 83-228 / NR / 79 / n/a >228 / NR / 78.8 / n/a Stat Method: ANOVA
		maternal urinary arsenic concentration (gestation week 8) (quartiles), µg/L Exp. Level / n / mean / (CI) 0-36 / NR / 81.2 / n/a 37-39 / NR / 79.5 / n/a 80-206 / NR / 79.1 / n/a >206 / NR / 78.6 / n/a Stat Method: ANOVA
		log10 maternal urinary arsenic concentration (gestation week 30; females), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -1.5 / -2.6, -0.4

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: linear regression
		log10 maternal urinary arsenic concentration (gestation week 30; males), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.06 / -1.0, 1.1 Stat Method: linear regression
		log10 maternal urinary arsenic concentration (gestation week 8; females), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -1.2 / -2.4, -0.06 Stat Method: linear regression
		log10 maternal urinary arsenic concentration (gestation week 8; males), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.6 / -1.7, 0.5 Stat Method: linear regression
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic levels measured in children at 1.5 and 5 years and characterized into quartiles; collected during home interviews; median urinary As: 35 µg/L and 51 µg/L at 1.5 and 5 years, respectively **Population-Level Exposure:** 0-120 µg/L range	**Outcome: full scale IQ (FSIQ) score**
		urinary arsenic concentration (at 1.5 years) (quartiles), µg/L Exp. Level / n / mean / (CI) 0-17 / NR / 77.1 / n/a 18-35 / NR / 74.9 / n/a 36-80 / NR / 74.1 / n/a >80 / NR / 74.3 / n/a Stat Method: ANOVA
		urinary arsenic concentration (at 5 years) (quartiles), µg/L Exp. Level / n / mean / (CI) 0-29 / NR / 76.6 / n/a 30-50 / NR / 75.6 / n/a 51-120 / NR / 74.1 / n/a >120 / NR / 74.3 / n/a Stat Method: ANOVA
		log10 urinary arsenic concentration (at 1.5 years; females), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.7 / -1.9, 0.4 Stat Method: linear regression
		log10 urinary arsenic concentration (at 5 years;

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		females), µg/L Exp. Level n adjBeta (CI) continuous NR -1.4 -2.7, -0.1 Stat Method: linear regression
		log10 urinary arsenic concentration (at 1.5 years; males), µg/L Exp. Level n adjBeta (CI) continuous NR -0.5 -1.6, 0.6 Stat Method: linear regression
		log10 urinary arsenic concentration (at 5 years; males), µg/L Exp. Level n adjBeta (CI) continuous NR 0.7 -0.5, 1.8 Stat Method: linear regression
		Outcome: performance intelligence quotient (PIQ)
		urinary arsenic concentration (at 1.5 years) (quartiles), µg/L Exp. Level n mean (CI) 0-17 NR 78 n/a 18-35 NR 76.2 n/a 36-80 NR 75.5 n/a >80 NR 75.7 n/a Stat Method: ANOVA
		urinary arsenic concentration (at 5 years) (quartiles), µg/L Exp. Level n mean (CI) 0-29 NR 77.2 n/a 30-50 NR 76.6 n/a 51-120 NR 75.6 n/a >120 NR 76 n/a Stat Method: ANOVA
		Outcome: verbal IQ (VIQ) score
		urinary arsenic concentration (at 1.5 years) (quartiles), µg/L Exp. Level n mean (CI) 0-17 NR 78 n/a 18-35 NR 76.2 n/a 36-80 NR 75.5 n/a >80 NR 75.7 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: ANOVA ***urinary arsenic concentration (at 5 years) (quartiles), µg/L*** Exp. Level / n / mean / (CI) 0-29 / NR / 81.6 / n/a 30-50 / NR / 80.1 / n/a 51-120 / NR / 78.8 / n/a >120 / NR / 78.8 / n/a Stat Method: ANOVA ***log10 urinary arsenic concentration (at 1.5 years; females), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.9 / -2.1, 0.4 Stat Method: linear regression ***log10 urinary arsenic concentration (at 5 years; females), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -2.4 / -3.8, -1.1 Stat Method: linear regression ***log10 urinary arsenic concentration (at 1.5 years; males), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1 / -2.1, 0.16 Stat Method: linear regression ***log10 urinary arsenic concentration (at 5 years; males), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.5 / -0.7, 1.7 Stat Method: linear regression
Hopenhayn et al. (2003) **Study Type:** cohort (prospective) **Location:** Chile (Antofagasta and Valparaiso)	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water samples collected in three households per city; water samples verified with local water company historical data; consistent exposure in each city verified using spot urine samples of subgroup of 19 women per city **Population-Level Exposure:**	**Outcome: birth weight** ***drinking water arsenic concentration by city of residence, µg/L*** Exp. Level / n / adjBeta / (CI) Valparaiso / NR / NR / n/a Antofagasta / NR / -57 / -123, 9 Stat Method: analysis of covariance; unclear which factors were adjusted for during analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Population: pregnant women aged 18 to 45 years enrolled at local clinics n exposed: 424 n reference: 420 n total: 844	0.5-40 µg/L range	
Huyck et al. (2007) **Study Type:** cohort (prospective) **Location:** Bangladesh (Sirajdikhan Upazila of the Munshiganj District) **Population:** pregnant women in proximity to Sirajdikhan Community Clinic n total: 49	**Exposure Surrogate:** hair **Exposure Description:** arsenic concentration in hair; samples collected using titanium nitride scissors; stored in paper envelopes; rinsed; external contamination of samples removed by sonication **Population-Level Exposure:** 0.09-3.28 µg/g range	**Outcome: birth weight** ***arsenic concentration in maternal hair at first visit, µg/g*** Exp. Level / n / adjOR / (CI) continuous / NR / 0.4 / 0.12, 1.35 Stat Method: logistic regression ***arsenic concentration in maternal hair within 2 weeks after birth, µg/g*** Exp. Level / n / adjOR / (CI) continuous / NR / 0.45 / 0.1, 2.04 Stat Method: logistic regression ***arsenic concentration in maternal hair at first visit, µg/g*** Exp. Level / n / adjBeta / (CI) continuous / NR / -193.5 / n/a Stat Method: multivariate linear regression
	Exposure Surrogate: toenails **Exposure Description:** arsenic concentration in toenails; samples collected using titanium nitride scissors; stored in paper envelopes; rinsed; external contamination of samples removed by sonication **Population-Level Exposure:** 0.19-8.04 µg/g range	**Outcome: birth weight** ***arsenic concentration in maternal nail at first visit, µg/g*** Exp. Level / n / adjOR / (CI) continuous / NR / 0.83 / 0.48, 1.42 Stat Method: logistic regression
Jin et al. (2013) **Study Type:** case-control	**Exposure Surrogate:** placenta **Exposure Description:** arsenic levels in placentas collected upon delivery/pregnancy termination	**Outcome: neural tube defects: anencephaly and spina bifida** ***arsenic concentration in placental samples, ng/g*** Exp. Level / n / adjOR / (CI) ≤ 8.93 / NR / NR / n/a >8.93 / NR / 0.88 / 0.43, 1.78

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Location: China (rural area of Shanxi Province) **Population:** Chinese women living in study area with newborns diagnosed with neural tube defects n cases: 80 n control: 50	**Population-Level Exposure:** 8.93 ng/g median	Stat Method: multivariate logistic regression analyses
Khan et al. (2012) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar (Haizadi, Uchitpur, and Khagkanda unions)) **Population:** Children enrolled in ongoing school intervention study at 14 elementary schools n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration in well-water samples from each child's home **Population-Level Exposure:** 119.5 µg/L mean 147.5SD	**Outcome: Bangla language score** ***water arsenic (dichotomized), µg/L*** Exp. Level n adjBeta (CI) dichotomized NR -1.71 -4.77, 1.34 Stat Method: spline regression models **Outcome: English language score** ***water arsenic (dichotomized), µg/L*** Exp. Level n adjBeta (CI) dichotomized NR -0.73 -4.32, 2.86 Stat Method: spline regression models **Outcome: math score** ***water arsenic (dichotomized), µg/L*** Exp. Level n adjBeta (CI) dichotomized NR 0.56 -2.98, 4.10 Stat Method: spline regression models
Kippler et al. (2012) **Study Type:** cross-sectional **Location:** Bangladesh (Matlab) **Population:** pregnant women and their children enrolled in Maternal and Infant Nutrition Interventions	**Exposure Surrogate:** urine **Exposure Description:** individual urine samples collected at gestational weeks 8 (range 6-14 weeks) and 30 (range 24-40 weeks); one sample below LOD **Population-Level Exposure:** 160 µg/L mean	**Outcome: abdominal circumference** ***log transformed urinary arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR 0.022 -0.024, 0.069 Stat Method: mixed effect linear regression, log transformed **Outcome: biparietal diameter** ***log transformed urinary arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.012 -0.047, 0.024 Stat Method: mixed effect linear regression,

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
of Matlab (MINIMat) visited monthly by community health research worker n cases: n/a n control: n/a		log transformed **Outcome: femur length** ***log transformed urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.0089 / -0.044, 0.027 Stat Method: mixed effect linear regression, log transformed **Outcome: head circumference** ***log transformed urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.0082 / -0.047, 0.031 Stat Method: mixed effect linear regression, log transformed **Outcome: occipito-frontal diameter** ***log transformed urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.01 / -0.045, 0.025 Stat Method: mixed effect linear regression, log transformed
Kwok et al. (2006) **Study Type:** cross-sectional **Location:** Bangladesh (Faridpur district (Faridpur Sadar upazila) and Chandpur district (Matlab and Shahrasti upazilas)) **Population:** residents of 261 highly arsenic-contaminated villages n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** water samples collected during in-home interview from main drinking water source used during pregnancy **Population-Level Exposure:** 0.5-668 ppb range	**Outcome: birth defects** ***drinking water arsenic concentration, ppb*** Exp. Level / n / adjOR / (CI) continuous / NR / 1.005 / 1.001, 1.010 Stat Method: multivariate logistic regression ***drinking water arsenic concentration, ppb*** Exp. Level / n / Prev / (CI) ≤ 10 / 2 / 0.6 / n/a 11-50 / 1 / 0.4 / n/a 51-100 / 1 / 0.5 / n/a 101-200 / 1 / 0.2 / n/a 201-300 / 2 / 0.4 / n/a >300 / 4 / 1.7 / n/a Stat Method: prevalence **Outcome: low birth weight** ***drinking water arsenic concentration, ppb***

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjOR / (CI) continuous / NR / 0.999 / 0.997, 1.000 Stat Method: multivariate logistic regression
		drinking water arsenic concentration, ppb Exp. Level / n / Prev / (CI) ≤ 10 / 40 / 12.3 / n/a 11-50 / 18 / 7.8 / n/a 51-100 / 17 / 7.8 / n/a 101-200 / 44 / 8.8 / n/a 201-300 / 53 / 10.7 / n/a >300 / 22 / 9.3 / n/a Stat Method: prevalence
		Outcome: stunting
		drinking water arsenic concentration, ppb Exp. Level / n / adjOR / (CI) continuous / NR / 1 / 1.00, 1.001 Stat Method: multivariate logistic regression
		drinking water arsenic concentration, ppb Exp. Level / n / Prev / (CI) ≤ 10 / 146 / 44.8 / n/a 11-50 / 102 / 44.3 / n/a 51-100 / 89 / 40.6 / n/a 101-200 / 256 / 51.3 / n/a 201-300 / 265 / 53.4 / n/a >300 / 146 / 61.9 / n/a Stat Method: prevalence
		Outcome: under-weight
		drinking water arsenic concentration, ppb Exp. Level / n / adjOR / (CI) continuous / NR / 1 / 0.999, 1.001 Stat Method: multivariate logistic regression
		drinking water arsenic concentration, ppb Exp. Level / n / Prev / (CI) ≤ 10 / 126 / 38.7 / n/a 11-50 / 86 / 37.4 / n/a 51-100 / 88 / 40.2 / n/a 101-200 / 227 / 45.5 / n/a 201-300 / 223 / 45 / n/a >300 / 124 / 52.5 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: prevalence
Milton et al. (2005) **Study Type:** cross-sectional **Location:** Bangladesh (Comilla, Chandpur, and Chuadanga districts) **Population:** women living in study area with ≥ 1 prior pregnancy n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** single well-water measurement used to characterize chronic arsenic exposure; arsenic concentrations recorded as zero replaced with 30 µg/L **Population-Level Exposure:** 279 µg/L mean 355SD	**Outcome: neonatal death** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 50 / 16 / 1 / n/a >50 / 70 / 1.8 / 0.9, 3.5 51-100 / 12 / 2.7 / 1.1, 6.73 >100 / 58 / 1.7 / 0.8, 3.3 Stat Method: logistic regression analysis
Nahar et al. (2014) **Study Type:** cross-sectional **Location:** Bangladesh (Sonargaon thana) **Population:** adolescents from highly arsenic-contaminated area n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** water samples from each respondent's tube well collected; half the detection limit used as the value for nondetects **Population-Level Exposure:** 71.7 µg/L mean	**Outcome: intelligence quotient (IQ) percentile** ***water arsenic concentration, µg/L*** Exp. Level / n / mean / (CI) 0.8-10 / NR / 52.2 / n/a 11-50 / NR / 43.4 / n/a 51-100 / NR / 44 / n/a >100 / NR / 40.7 / n/a Stat Method: one-way ANOVA, ANCOVA
		Outcome: social competence (SC) score ***water arsenic concentration, µg/L*** Exp. Level / n / mean / (CI) 0.8-10 / NR / 38.6 / n/a 11-50 / NR / 37.6 / n/a 51-100 / NR / 36.1 / n/a >100 / NR / 35.9 / n/a Stat Method: one-way ANOVA, ANCOVA
	Exposure Surrogate: urine **Exposure Description:** spot urine samples collected for measurement of As; half the detection limit used as the value for nondetects	**Outcome: intelligence quotient (IQ) percentile** ***urinary arsenic concentration, µg/L*** Exp. Level / n / mean / (CI) 1-137 / NR / 50.5 / n/a 138-400 / NR / 40.6 / n/a 401-1,312 / NR / 40.9 / n/a Stat Method: one-way ANOVA, ANCOVA

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
	Population-Level Exposure: 205.3 µg/L mean	**Outcome: social competence (SC) score** ***urinary arsenic concentration, µg/L*** Exp. Level / n / mean / (CI) 1-137 / NR / 39 / n/a 138-400 / NR / 35.2 / n/a 401-1,312 / NR / 34.7 / n/a Stat Method: one-way ANOVA, ANCOVA
Parvez et al. (2011) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** children 8-11 years old living in households within the HEALS cohort of villages n cases: n/a n control: n/a	**Exposure Surrogate:** blood **Exposure Description:** venous whole blood samples collected at field clinic and analyzed for Pb, Mn, Se, and As concentrations **Population-Level Exposure:** 4.8 µg/L mean 3.2SD	**Outcome: body coordination** ***blood arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1.61 / -2.70, -0.51 Stat Method: linear regression, log transformed **Outcome: fine manual control** ***blood arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1.68 / -3.19, -0.18 Stat Method: linear regression, log transformed **Outcome: manual coordination** ***blood arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.49 / -1.73, 0.76 Stat Method: linear regression, log transformed **Outcome: strength and agility** ***blood arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.15 / -0.57, 0.86 Stat Method: linear regression, log transformed **Outcome: total motor composite** ***blood arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -3.63 / -6.72, -0.54 Stat Method: linear regression, log transformed

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Surrogate: drinking water **Exposure Description:** water samples collected from wells of use and analyzed for As and Mn concentrations **Population-Level Exposure:** 43.3 µg/L mean 73.6SD	**Outcome: body coordination** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.43 -0.77, -0.06 Stat Method: linear regression, log transformed **Outcome: fine manual control** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.54 -1.03, -0.05 Stat Method: linear regression, log transformed **Outcome: manual coordination** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.15 -0.52, 0.30 Stat Method: linear regression, log transformed **Outcome: strength and agility** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.11 -0.28, 0.18 Stat Method: linear regression, log transformed **Outcome: total motor composite** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -1.18 -2.13, -0.10 Stat Method: linear regression, log transformed
	Exposure Surrogate: toenails **Exposure Description:** toenails collected from individuals and cleaned prior to analysis **Population-Level Exposure:**	**Outcome: body coordination** ***toenail arsenic concentration, µg/g*** Exp. Level n adjBeta (CI) continuous NR -1.86 -2.83, -0.89 Stat Method: linear regression, log transformed **Outcome: fine manual control**

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
	5.9 µg/g mean 6.3SD	***toenail arsenic concentration, µg/g*** Exp. Level n adjBeta (CI) continuous NR -0.84 -2.20, 0.50 Stat Method: linear regression, log transformed
		Outcome: manual coordination
		toenail arsenic concentration, µg/g Exp. Level n adjBeta (CI) continuous NR -0.68 -1.80, 0.42 Stat Method: linear regression, log transformed
		Outcome: strength and agility
		toenail arsenic concentration, µg/g Exp. Level n adjBeta (CI) continuous NR -0.38 -1.02, 0.25 Stat Method: linear regression, log transformed
		Outcome: total motor composite
		toenail arsenic concentration, µg/g Exp. Level n adjBeta (CI) continuous NR -3.77 -6.52, -1.03 Stat Method: linear regression, log transformed
	Exposure Surrogate: urine **Exposure Description:** urine samples collected and analyzed for urinary As concentrations **Population-Level Exposure:** 246.5 g creatinine/L mean 183.9SD	**Outcome: body coordination**
		creatinine adjusted urinary arsenic concentration, g creatinine/L Exp. Level n adjBeta (CI) continuous NR -1.6 -2.61, -0.60 Stat Method: linear regression, log transformed
		urinary arsenic concentration, µg/L Exp. Level n adjBeta (CI) continuous NR -1.43 -2.67, -0.61 Stat Method: linear regression, log transformed
		Outcome: fine manual control
		creatinine adjusted urinary arsenic concentration, g creatinine/L

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level n adjBeta (CI) continuous NR -0.88 -2.28, 0.51 Stat Method: linear regression, log transformed
		urinary arsenic concentration, µg/L Exp. Level n adjBeta (CI) continuous NR -1.03 -2.45, 0.39 Stat Method: linear regression, log transformed
		Outcome: manual coordination
		creatinine adjusted urinary arsenic concentration, g creatinine/L Exp. Level n adjBeta (CI) continuous NR -0.76 -1.91, 0.38 Stat Method: linear regression, log transformed
		urinary arsenic concentration, µg/L Exp. Level n adjBeta (CI) continuous NR -0.73 -1.89, 0.44 Stat Method: linear regression, log transformed
		Outcome: strength and agility
		creatinine adjusted urinary arsenic concentration, g creatinine/L Exp. Level n adjBeta (CI) continuous NR -0.16 -0.83, 0.49 Stat Method: linear regression, log transformed
		urinary arsenic concentration, µg/L Exp. Level n adjBeta (CI) continuous NR -0.19 -0.86, 0.48 Stat Method: linear regression, log transformed
		Outcome: total motor composite
		creatinine adjusted urinary arsenic concentration, g creatinine/L Exp. Level n adjBeta (CI) continuous NR -3.42 -6.27, -0.57 Stat Method: linear regression, log

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		transformed ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -3.59 / -6.50, -0.68 Stat Method: linear regression, log transformed
Rahman et al. (2007) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** residents with pregnancies between 1991-2000 n total: 29,134	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in all functioning tube wells for each household sampled; exposure stratified by quintiles **Population-Level Exposure:** 239 µg/L mean	**Outcome: fetal loss** ***arsenic water concentration during gestation (quintiles), µg/L*** Exp. Level / n / RR / (CI) <10 / 464 / 1 / n/a 10-166 / 453 / 0.98 / 0.86, 1.11 167-276 / 488 / 1.05 / 0.93, 1.20 277-408 / 528 / 1.14 / 1.01, 1.30 ≥ 409 / 511 / 1.1 / 0.97, 1.25 Stat Method: logistic regression **Outcome: infant death** ***arsenic water concentration following birth (quintiles), µg/L*** Exp. Level / n / adjRR / (CI) <10 / 229 / 1 / n/a 10-163 / 269 / 1.13 / 0.95, 1.35 164-275 / 282 / 1.19 / 1, 1.42 276-408 / 308 / 1.29 / 1.08, 1.53 ≥ 409 / 285 / 1.19 / 1, 1.41 Stat Method: logistic regression **Outcome: neonatal death** ***arsenic water concentration following birth (quintiles), µg/L*** Exp. Level / n / RR / (CI) <10 / NR / 1 / n/a 10-163 / NR / 1.11 / 0.89, 1.38 164-275 / NR / 1.18 / 0.95, 1.47 276-408 / NR / 1.17 / 0.94, 1.46 ≥ 409 / NR / 1.21 / 0.98, 1.50 Stat Method: logistic regression **Outcome: postneonatal death** ***arsenic water concentration following birth (quintiles), µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjRR / (CI) <10 / NR / 1 / n/a 10-163 / NR / 1.22 / 0.91, 1.63 164-275 / NR / 1.26 / 0.94, 1.69 276-408 / NR / 1.55 / 1.17, 2.05 ≥ 409 / NR / 1.22 / 0.91, 1.63 Stat Method: logistic regression
Rahman et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** residents pregnant between 2001-2003 and their newborn children n total: 1,578	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentrations in samples obtained during gestation; calculated as the sum of inorganic arsenic and methylated metabolites and adjusted by specific gravity; concentration reported as average of GW 8 and 30 **Population-Level Exposure:** 160 µg/L mean 163SD	**Outcome: birth length** ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.06 / n/a Stat Method: least-squared linear regression (beta coefficient)
		Outcome: birth weight ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1.68 / n/a Stat Method: least-squared linear regression (beta coefficient)
		Outcome: chest circumference ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.14 / n/a Stat Method: least-squared linear regression (beta coefficient)
		Outcome: head circumference ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.05 / n/a Stat Method: least-squared linear regression (beta coefficient)
Rahman et al. (2010) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab)	**Exposure Surrogate:** urine **Exposure Description:** urine samples collected at ~approx gestation week 8 and gestation week 30; samples adjusted by specific gravity rather than creatinine; urine levels divided into quintiles	**Outcome: infant death** ***average urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / HR / (CI) <38 / 3 / 1 / n/a 39-67 / 6 / 1.78 / 0.44, 7.16 68-133 / 6 / 1.83 / 0.45, 7.35 134-267 / 7 / 2.29 / 0.58, 9.05

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Population: pregnant women enrolled in the Maternal and Infant Nutrition Intervention in Matlab study (MINIMat) n total: 1,725	**Population-Level Exposure:** 38-2,019 µg/L range	268-2,019 14 5.01 1.41, 17.84 Stat Method: Cox proportional hazard models
Rocha-Amador et al. (2007) **Study Type:** cross-sectional **Location:** Mexico (Moctezuma, Salitral, and 5 de Febrero communities) **Population:** children in rural communities exposed to range of arsenic drinking water levels n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration in tap and bottled water sampled at each individual's home on same day as outcome evaluations **Population-Level Exposure:** not available	**Outcome: full IQ** ***log transformed arsenic concentration in water, µg/L*** Exp. Level n adjBeta (CI) continuous NR -6.15 n/a Stat Method: multiple linear regression **Outcome: Performance IQ** ***log transformed arsenic concentration in water, µg/L*** Exp. Level n adjBeta (CI) continuous NR -4.3 n/a Stat Method: multiple linear regression **Outcome: Verbal IQ** ***log transformed arsenic concentration in water, µg/L*** Exp. Level n adjBeta (CI) continuous NR -6.4 n/a Stat Method: multiple linear regression
	Exposure Surrogate: urine **Exposure Description:** arsenic concentrations in urine collected same day as neuropsychological evaluations; arsenic level adjusted for urinary creatinine **Population-Level Exposure:** not available	**Outcome: full IQ** ***log transformed urinary arsenic concentration, µg/g-creatinine*** Exp. Level n adjBeta (CI) continuous NR -5.72 n/a Stat Method: multiple linear regression **Outcome: Performance IQ** ***log transformed urinary arsenic concentration, µg/g-creatinine*** Exp. Level n adjBeta (CI) continuous NR -4.19 n/a Stat Method: multiple linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: Verbal IQ ***log transformed urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjBeta / (CI) continuous / NR / -5.5 / n/a Stat Method: multiple linear regression
Roy et al. (2011) **Study Type:** cross-sectional **Location:** Mexico (Torreon) **Population:** first-grade children attending school near a metal foundry n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** total urinary arsenic measured as the sum inorganic arsenic and all arsenic metabolites (MMA, DMA); first morning urine samples collected after an overnight fast; exposure stratified by quartiles **Population-Level Exposure:** 55.2 µg/L median	**Outcome: ADHD index** ***total urinary arsenic concentration (quartiles), µg/L*** Exp. Level / n / adjBeta / (CI) 7.7-35.9 / NR / NR / n/a 36-55.2 / NR / 1.8 / -0.7, 4.3 55.3-75.6 / NR / 2.2 / -0.3, 4.6 75.7-215.9 / NR / 2.1 / -0.4, 4.7 Stat Method: linear regression
		total urinary arsenic concentration (quartiles), µg/L Exp. Level / n / adjOR / (CI) 7.7-35.9 / NR / 1 / n/a 36-55.2 / NR / 1.4 / 0.6, 3.2 55.3-75.6 / NR / 2.4 / 1.1, 4.9 75.7-215.9 / NR / 1.9 / 0.9, 4.3 Stat Method: logistic regression, behavior modeled as a categorical variable (T-score <65 vs. T-score ≥ 65)
		Outcome: cognitive problems ***total urinary arsenic concentration (quartiles), µg/L*** Exp. Level / n / adjBeta / (CI) 7.7-35.9 / NR / NR / n/a 36-55.2 / NR / 1.6 / -1.1, 4.3 55.3-75.6 / NR / 2.7 / -0.05, 5.4 75.7-215.9 / NR / 2.6 / -0.2, 5.4 Stat Method: linear regression
		total urinary arsenic concentration (quartiles), µg/L Exp. Level / n / adjOR / (CI) 7.7-35.9 / NR / 1 / n/a 36-55.2 / NR / 1.3 / 0.6, 2.6 55.3-75.6 / NR / 1.4 / 0.7, 2.7

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		75.7-215.9 NR 1.5 0.8, 3.1 Stat Method: logistic regression, behavior modeled as a categorical variable (T-score <65 vs. T-score ≥ 65)
		Outcome: hyperactive behavior
		total urinary arsenic concentration (quartiles), µg/L Exp. Level / n / adjBeta / (CI) 7.7-35.9 NR NR n/a 36-55.2 NR 1.8 -0.9, 4.6 55.3-75.6 NR 1.6 -1.2, 4.3 75.7-215.9 NR 2.1 -0.7, 4.9 Stat Method: linear regression
		total urinary arsenic concentration (quartiles), µg/L Exp. Level / n / adjOR / (CI) 7.7-35.9 NR 1 n/a 36-55.2 NR 1.4 0.7, 2.7 55.3-75.6 NR 1.6 0.8, 3.2 75.7-215.9 NR 1.4 0.7, 2.9 Stat Method: logistic regression, behavior modeled as a categorical variable (T-score <65 vs. T-score ≥ 65)
		Outcome: oppositional behavior
		total urinary arsenic concentration (quartiles), µg/L Exp. Level / n / adjBeta / (CI) 7.7-35.9 NR NR n/a 36-55.2 NR 3.1 0.01, 6.1 55.3-75.6 NR 2.5 -0.5, 5.6 75.7-215.9 NR 2.1 -1.1, 5.2 Stat Method: linear regression
		total urinary arsenic concentration (quartiles), µg/L Exp. Level / n / adjOR / (CI) 7.7-35.9 NR 1 n/a 36-55.2 NR 2.1 1.0, 4.4 55.3-75.6 NR 1.8 0.9, 3.8 75.7-215.9 NR 2 1.0, 4.3 Stat Method: logistic regression, behavior modeled as a categorical variable (T-score

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		<65 vs. T-score ≥ 65)
Saha et al. (2012) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** infants born in a population-based intervention trial in rural area n total: 2,372	**Exposure Surrogate:** urine **Exposure Description:** maternal urine samples collected 8 or 30 weeks of pregnancy; urine samples collected from children at 18 months of age; arsenic exposure stratified by quintiles **Population-Level Exposure:** 66.8 µg/L mean, 87.7SD, 11.7-159 µg/L 10th percentile	**Outcome: attained length (cm) at 18 months of age** ***child urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjBeta / (CI) 2.4-16 / NR / 1 / n/a 16-26 / NR / 0.16 / -0.21, 0.53 26-46 / NR / -0.28 / -0.65, 0.093 46-96 / NR / -0.024 / -0.39, 0.35 96-937 / NR / 0.18 / -0.20, 0.55 Stat Method: multivariate logistic regression **Outcome: attained length (cm) at 24 months of age** ***child urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjBeta / (CI) 2.4-16 / NR / 1 / n/a 16-26 / NR / 0.16 / -0.25, 0.57 26-46 / NR / -0.18 / -0.59, 0.23 46-96 / NR / -0.26 / -0.67, 0.15 96-937 / NR / -0.013 / -0.43, 0.40 Stat Method: multivariate logistic regression ***maternal urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjBeta / (CI) 1.2-33 / NR / 1 / n/a 33-57 / NR / -0.098 / -0.53, 0.34 57-115 / NR / -0.22 / -0.65, 0.22 116-245 / NR / -0.15 / -0.59, 0.28 246-1,611 / NR / 0.29 / -0.15, 0.73 Stat Method: multivariate logistic regression **Outcome: attained length (cm) at 3 months of age** ***maternal urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjBeta / (CI) 1.2-33 / NR / 1 / n/a 33-57 / NR / 0.21 / -0.13, 0.56 57-115 / NR / -0.067 / -0.41, 0.28

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		116-245 NR 0.094 -0.27, 0.45 246-1,611 NR 0.26 -0.096, 0.61 Stat Method: multivariate logistic regression
		Outcome: attained weight (kg) at 18 months of age
		child urinary arsenic concentration (quintiles), µg/L Exp. Level / n / adjBeta / (CI) 2.4-16 NR 1 n/a 16-26 NR -0.097 -0.23, 0.038 26-46 NR -0.18 -0.32, -0.047 46-96 NR -0.19 -0.33, -0.57 96-937 NR -0.059 -0.20, 0.076 Stat Method: multivariate logistic regression
		Outcome: attained weight (kg) at 24 months of age
		child urinary arsenic concentration (quintiles), µg/L Exp. Level / n / adjBeta / (CI) 2.4-16 NR 1 n/a 16-26 NR -0.027 -0.18, 0.12 26-46 NR -0.13 -0.28, 0.019 46-96 NR -0.082 -0.23, 0.067 96-937 NR 0.005 -0.14, 0.16 Stat Method: multivariate logistic regression
		maternal urinary arsenic concentration (quintiles), µg/L Exp. Level / n / adjBeta / (CI) 1.2-33 NR 1 n/a 33-57 NR -0.015 -0.17, 0.14 57-115 NR -0.092 -0.25, 0.062 116-245 NR -0.06 -0.22, 0.094 246-1,611 NR 0.044 -0.11, 0.20 Stat Method: multivariate logistic regression
		Outcome: attained weight (kg) at 3 months of age
		maternal urinary arsenic concentration (quintiles), µg/L Exp. Level / n / adjBeta / (CI) 1.2-33 NR 1 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		33-57 NR 0.11 0.006, 0.21 57-115 NR -0.017 -0.12, 0.086 116-245 NR 0.089 -0.019, 0.20 246-1,611 NR 0.078 -0.028, 0.18 Stat Method: multivariate logistic regression
Tofail et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** MINIMat study cohort n total: 1,799	**Exposure Surrogate:** urine **Exposure Description:** spot urine samples collected from mothers at home at time of pregnancy testing (on average gestational week 8) and at clinic (during 30th gestational week); arsenic concentrations adjusted for variation in urine dilution by specific gravity **Population-Level Exposure:** 82.5 µg/L median	**Outcome: "Cover" Problem Solving Test** ***mothers' urinary arsenic (mean of gestation week 8 and 30), µg/L*** Exp. Level n adjBeta (CI) continuous NR 0.4 -0.4, 1.3 Stat Method: multiple regression **Outcome: "Support" Problem Solving Test** ***mothers' urinary arsenic (mean of gestation week 8 and 30), µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.6 -1.5, 0.4 Stat Method: multiple regression **Outcome: Psychomotor Development Index (PDI)** ***mothers' urinary arsenic (mean of gestation week 8 and 30), µg/L*** Exp. Level n adjBeta (CI) continuous NR 0.9 -0.9, 2.7 Stat Method: multiple regression
Tsai et al. (2003) **Study Type:** cross-sectional **Location:** Taiwan (Ilan county: Chiaohsi, Chuangwei, Wuchieh, and Tungshan townships) **Population:** adolescents with chronic exposure to arsenic in drinking	**Exposure Surrogate:** drinking water **Exposure Description:** individual cumulated arsenic exposure for exposed individuals calculated from household arsenic concentration in well water, duration of drinking well water, and averaged water intake per day; Taiwan Environmental Protection Agency reported mean tap water arsenic concentrations in control area <1 ppb, so control arsenic exposure omitted because levels too low to be calculated accurately **Population-Level Exposure:**	**Outcome: continuous performance test** ***cumulative arsenic exposure, ppm*** Exp. Level n adjBeta (CI) - NR 0 n/a 2,047.7–43,882.13 NR 95.32 n/a 64,377.79–2,419,950 NR 35.26 n/a Stat Method: multiple linear regression ***cumulative arsenic exposure, ppm*** Exp. Level n mean (CI) - NR 443.81 n/a 2,047.7–43,882.13 NR 535.7 n/a 64,377.79–2,419,950 NR 480.61 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
water n cases: 49 n control: 60	2,047.7-2,419,950 ppm range	Stat Method: one-way ANOVA, Scheffe's test **Outcome: pattern memory** ***cumulative arsenic exposure, ppm*** Exp. Level / n / adjBeta / (CI) - / NR / 0 / n/a 2,047.7–43,882.13 / NR / 470.06 / n/a 64,377.79–2,419,950 / NR / 965.92 / n/a Stat Method: multiple linear regression ***cumulative arsenic exposure, ppm*** Exp. Level / n / mean / (CI) - / NR / 4972.24 / n/a 2,047.7–43,882.13 / NR / 5437.05 / n/a 64,377.79–2,419,950 / NR / 5961.03 / n/a Stat Method: one-way ANOVA, Scheffe's test **Outcome: switching attention** ***cumulative arsenic exposure, ppm*** Exp. Level / n / adjBeta / (CI) - / NR / 0 / n/a 2,047.7–43,882.13 / NR / 184.09 / n/a 64,377.79–2,419,950 / NR / 234.78 / n/a Stat Method: multiple linear regression ***cumulative arsenic exposure, ppm*** Exp. Level / n / mean / (CI) - / NR / 635.11 / n/a 2,047.7–43,882.13 / NR / 801.6 / n/a 64,377.79–2,419,950 / NR / 861.13 / n/a Stat Method: one-way ANOVA, Scheffe's test **Outcome: symbol digit** ***cumulative arsenic exposure, ppm*** Exp. Level / n / adjBeta / (CI) - / NR / 0 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		2,047.7–43,882.13 NR 7.02 n/a 64,377.79–2,419,950 NR 15.97 n/a Stat Method: multiple linear regression
		cumulative arsenic exposure, ppm Exp. Level / n / mean / (CI) - NR 223.44 n/a 2,047.7–43,882.13 NR 230.6 n/a 64,377.79–2,419,950 NR 242.56 n/a Stat Method: one-way ANOVA, Scheffe's test
Vall et al. (2012) **Study Type:** cross-sectional **Location:** Spain (Tenerife) **Population:** Mother-child pairs in study area n cases: n/a n control: n/a	**Exposure Surrogate:** meconium **Exposure Description:** neonatal meconium collected from infant's diaper **Population-Level Exposure:** 6.79 ppb mean 1.05SD	**Outcome: birth weight**
		arsenic concentration in meconium, ppb Exp. Level / n / OR / (CI) arsenic detected NR 1 1.00, 1.02 arsenic non-detected NR NR n/a Stat Method: odd ratio; chi-square
		Outcome: cranial perimeter
		arsenic concentration in meconium, ppb cranial perimeter not significantly associated with arsenic in meconium
		Outcome: gestational age at birth
		arsenic concentration in meconium, ppb gestational age at birth not significantly associated with arsenic in meconium
		Outcome: length
		arsenic concentration in meconium, ppb length not significantly associated with arsenic in meconium
		Outcome: prematurity
		arsenic concentration in meconium, ppb prematurity not significantly associated with arsenic in meconium
Von Ehrenstein et al. (2006)	**Exposure Surrogate:** drinking water	**Outcome: infant mortality**
		arsenic concentration in drinking water, µg/L

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cross-sectional **Location:** India (West Bengal) **Population:** women residing in 21 villages of West Bengal, India. n cases: n/a n control: n/a	**Exposure Description:** water samples collected from tube wells used at least 6 months since first pregnancy; past arsenic concentration measurements used when wells were closed **Population-Level Exposure:** 0-200 µg/L range	Exp. Level / n / adjOR / (CI) 0-49 / 13 / 1 / n/a 50-199 / 2 / 0.82 / 0.13, 5.25 ≥ 200 / 4 / 1.33 / 0.43, 4.04 Stat Method: logistic regression based on method of generalized estimating equations **Outcome: neonatal death** ***arsenic concentration in drinking water, µg/L*** Exp. Level / n / adjOR / (CI) 0-49 / 5 / 1 / n/a 50-199 / 1 / 1.21 / 0.09, 15.4 ≥ 200 / 4 / 2.81 / 0.73, 10.8 Stat Method: logistic regression based on method of generalized estimating equations
von Ehrenstein et al. (2007) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** children of women participating in pregnancy outcomes associated with arsenic in drinking water study n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** samples from all tube wells used by participants for at least 6 months collected; population-level exposure represents average lifetime water exposure; peak exposure (147 +/- 322 µg/L) was highest known annual average water concentration of arsenic ingested by a child; prenatal arsenic exposure based on the mother's drinking water arsenic exposure during pregnancy **Population-Level Exposure:** 59 µg/L mean, 133SD, 1-870 µg/L range	**Outcome: block design** ***average pregnancy arsenic concentration in drinking water, µg/L*** Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.09 / -0.34, 0.17 50-99 / NR / 0.12 / -0.25, 0.49 ≥ 100 / NR / -0.01 / -0.26, 0.23 Stat Method: linear regression ***average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.02 / -0.05, 0.02 Stat Method: linear regression ***peak lifetime arsenic concentration in drinking water, µg/L*** Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.01 / -0.25, 0.23 50-99 / NR / 0.05 / -0.33, 0.44 ≥ 100 / NR / -0.02 / -0.23, 0.22 Stat Method: linear regression ***peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.02 / -0.02, 0.05

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: linear regression
		Outcome: coding
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.13 / -0.48, 0.21 50-99 / NR / -0.08 / -0.51, 0.36 ≥ 100 / NR / 0.031 / -0.21, 0.27 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.01 / -0.03, 0.04 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.14 / -0.47, 0.20 50-99 / NR / -0.03 / -0.48, 0.43 ≥ 100 / NR / -0.13 / -0.37, 0.11 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.01 / -0.02, 0.04 Stat Method: linear regression
		Outcome: colored progressive matrices
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.08 / -0.36, 0.20 50-99 / NR / -0.07 / -0.38, 0.24 ≥ 100 / NR / -0.07 / -0.30, 0.17 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjBeta / (CI) continuous / NR / 0 / -0.03, 0.03 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.02 / -0.28, 0.24 50-99 / NR / -0.29 / -0.57, -0.02 ≥ 100 / NR / -0.02 / -0.28, 0.24 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.01 / -0.02, 0.04 Stat Method: linear regression
		Outcome: digit span
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / 0.08 / -0.24, 0.40 50-99 / NR / 0.09 / -0.36, 0.54 ≥ 100 / NR / -0.06 / -0.30, 0.19 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.01 / -0.02, 0.04 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / 0.08 / -0.24, 0.40 50-99 / NR / -0.15 / -0.54, 0.23 ≥ 100 / NR / -0.08 / -0.32, 0.17 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level n adjBeta (CI) continuous NR 0.02 -0.01, 0.05 Stat Method: linear regression
		Outcome: full scale
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level n adjBeta (CI) <10 NR 1 n/a 10-49 NR -0.047 -0.38, 0.28 50-99 NR -0.007 -0.36, 0.34 ≥ 100 NR -0.002 -0.24, 0.24 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level n adjBeta (CI) continuous NR 0.01 -0.02, 0.03 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level n adjBeta (CI) <10 NR 1 n/a 10-49 NR 0.006 -0.31, 0.33 50-99 NR -0.16 -0.56, 0.23 ≥ 100 NR -0.06 -0.30, 0.18 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level n adjBeta (CI) continuous NR -0.02 -0.02, 0.05 Stat Method: linear regression
		Outcome: object assembly
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level n adjBeta (CI) <10 NR 1 n/a 10-49 NR 0.079 -0.31, 0.47 50-99 NR 0.12 -0.28, 0.51 ≥ 100 NR 0.17 -0.09, 0.42 Stat Method: linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.02 / -0.01, 0.06 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / 0.16 / -0.23, 0.55 50-99 / NR / 0.014 / -0.43, 0.46 ≥ 100 / NR / 0.06 / -0.18, 0.31 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.02 / -0.02, 0.06 Stat Method: linear regression
		Outcome: pegboard
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.18 / -0.44, 0.09 50-99 / NR / 0.09 / -0.29, 0.48 ≥ 100 / NR / -0.03 / -0.23, 0.17 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0 / -0.02, 0.03 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.1 / -0.39, 0.19 50-99 / NR / 0.13 / -0.27, 0.53 ≥ 100 / NR / 0.06 / -0.14, 0.26 Stat Method: linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level n adjBeta (CI) continuous NR 0.01 -0.02, 0.003 Stat Method: linear regression
		Outcome: picture completion
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level n adjBeta (CI) <10 NR 1 n/a 10-49 NR 0.08 -0.24, 0.40 50-99 NR -0.25 -0.58, 0.09 ≥ 100 NR -0.06 -0.29, 0.17 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level n adjBeta (CI) continuous NR -0.01 -0.04, 0.02 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level n adjBeta (CI) <10 NR 1 n/a 10-49 NR 0.12 -0.19, 0.43 50-99 NR -0.45 -0.84, -0.07 ≥ 100 NR -0.09 -0.33, 0.14 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level n adjBeta (CI) continuous NR 0 -0.03, 0.04 Stat Method: linear regression
		Outcome: total sentence recall
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level n adjBeta (CI) <10 NR 1 n/a 10-49 NR 0.03 -0.24, 0.31 50-99 NR 0.32 -0.04, 0.69 ≥ 100 NR -0.05 -0.30, 0.19

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.03 / -0.07, 0.01 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / 0.11 / -0.19, 0.41 50-99 / NR / 0.28 / -0.08, 0.64 ≥ 100 / NR / -0.03 / -0.27, 0.21 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.03 / -0.05, 0 Stat Method: linear regression
		Outcome: vocabulary
		average pregnancy arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.23 / -0.54, 0.08 50-99 / NR / -0.036 / -0.40, 0.33 ≥ 100 / NR / -0.08 / -0.26, 0.53 Stat Method: linear regression
		average pregnancy arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.01 / -0.03, 0.06 Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water, µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 1 / n/a 10-49 / NR / -0.17 / -0.48, 0.14 50-99 / NR / -0.23 / -0.59, 0.12 ≥ 100 / NR / -0.05 / -0.29, 0.20

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: linear regression
		peak lifetime arsenic concentration in drinking water (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.01 / -0.02, 0.04 Stat Method: linear regression
	Exposure Surrogate: urine **Exposure Description:** child urine samples collected during physical examination and stratified in tertiles (tertile concentration data not reported) **Population-Level Exposure:** 78 µg/L mean, 61SD, 2-375 µg/L range	**Outcome: block design**
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.02 / -0.2, 0.2 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / 0.076 / -0.16, 0.31 ~ >82.6 and ~ >86.1 / NR / -0.085 / -0.34, 0.17 Stat Method: linear regression
		Outcome: coding
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.06 / -0.2, 0.09 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / -0.14 / -0.37, 0.10 ~ >82.6 and ~ >86.1 / NR / -0.13 / -0.38, 0.12 Stat Method: linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: colored progressive matrices
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.07 / -0.2, 0.07 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / 0.0009 / -0.22, 0.23 ~ >82.6 and ~ >86.1 / NR / -0.12 / -0.36, 0.11 Stat Method: linear regression
		Outcome: digit span
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.04 / -0.1, 0.2 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / -0.04 / -0.30, 0.22 ~ >82.6 and ~ >86.1 / NR / -0.0004 / -0.27, 0.27 Stat Method: linear regression
		Outcome: full scale
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.07 / -0.2, 0.09 Stat Method: linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / -0.11 / -0.34, 0.12 ~ >82.6 and ~ >86.1 / NR / -0.2 / -0.44, 0.03 Stat Method: linear regression
		Outcome: object assembly
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.07 / -0.2, 0.1 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / -0.16 / -0.34, 0.06 ~ >82.6 and ~ >86.1 / NR / -0.24 / -0.49, 0.01 Stat Method: linear regression
		Outcome: pegboard
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.04 / -0.1, 0.2 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ / NR / 0.15 / -0.07, 0.36

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		>44.2-<86.1 ~ >82.6 and ~ >86.1 NR 0.09 -0.14, 0.32 Stat Method: linear regression
		Outcome: picture completion
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous NR -0.1 -0.3, 0.04 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 NR 1 n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 NR -0.15 -0.34, 0.09 ~ >82.6 and ~ >86.1 NR -0.26 -0.51, -0.01 Stat Method: linear regression
		Outcome: total sentence recall
		child urinary arsenic concentration (per 100 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous NR 0.04 -0.1, 0.2 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 NR 1 n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 NR 0.23 0.02, 0.44 ~ >82.6 and ~ >86.1 NR 0.13 -0.09, 0.35 Stat Method: linear regression
		Outcome: vocabulary
		child urinary arsenic concentration (per 100

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.09 / -0.3, 0.07 Stat Method: linear regression
		child urinary arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) ~ <44.2 - <43.6 / NR / 1 / n/a ~ >43.6 - <82.6 and ~ >44.2-<86.1 / NR / -0.14 / -0.37, 0.10 ~ >82.6 and ~ >86.1 / NR / -0.28 / -0.55, -0.008 Stat Method: linear regression
Wasserman et al. (2004) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** children 10 years old residing in villages within the HEALS cohort n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in 196 tube wells used for drinking water at each residence; exposure levels split into quartiles **Population-Level Exposure:** 117.8 µg/L mean 145.2SD	**Outcome: full scale raw score** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1.64 / n/a Stat Method: linear regression analysis
		drinking water arsenic concentration (quartiles), µg/L Exp. Level / n / adjBeta / (CI) 0.1 - 5.5 / NR / NR / n/a 5.6 - 50.0 / NR / NR / n/a 50.1 - 176 / NR / -7.8 / n/a 177 - 790 / NR / -11.3 / n/a Stat Method: linear regression analysis
		Outcome: performance raw score ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -1.45 / n/a Stat Method: linear regression analysis
		drinking water arsenic concentration (quartiles), µg/L Exp. Level / n / adjBeta / (CI) 0.1 - 5.5 / NR / NR / n/a 5.6 - 50.0 / NR / NR / n/a 50.1 - 176 / NR / -7.3 / n/a 177 - 790 / NR / -9.7 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: linear regression analysis **Outcome: verbal raw score** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.19 n/a Stat Method: linear regression analysis ***drinking water arsenic concentration (quartiles), µg/L*** Exp. Level n adjBeta (CI) 0.1 - 5.5 NR NR n/a 5.6 - 50.0 NR NR n/a 50.1 - 176 NR NR n/a 177 - 790 NR -1.6 n/a Stat Method: linear regression analysis
	Exposure Surrogate: urine **Exposure Description:** arsenic concentration in urine, adjusted for urinary creatinine levels **Population-Level Exposure:** 116.6 µg/L mean 148.8SD	**Outcome: full scale raw score** ***urinary arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -2.9 n/a Stat Method: linear regression analysis **Outcome: performance raw score** ***urinary arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -2.2 n/a Stat Method: linear regression analysis **Outcome: verbal raw score** ***urinary arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.7 n/a Stat Method: linear regression analysis
Wasserman et al. (2007) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar)	**Exposure Surrogate:** drinking water **Exposure Description:** water samples from each home collected during survey of all wells in study region; **Population-Level Exposure:** 120.1 µg/L mean 134.4SD	**Outcome: full scale raw score** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -1.06 n/a Stat Method: linear regression analysis **Outcome: performance raw score** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Population: 6-year-old children of parents enrolled in the HEALS cohort study n cases: n/a n control: n/a		continuous NR -0.48 n/a Stat Method: linear regression analysis **Outcome: processing speed raw score** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.54 n/a Stat Method: linear regression analysis **Outcome: verbal raw score** ***drinking water arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.18 n/a Stat Method: linear regression analysis
	Exposure Surrogate: urine **Exposure Description:** each child provided urine specimens for measurement of urinary As; levels of As in urine adjusted for urinary creatinine levels **Population-Level Exposure:** 110.7 µg/g-creatinine mean 132.8SD	**Outcome: full scale raw score** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level n adjBeta (CI) continuous NR -1.78 n/a Stat Method: linear regression analysis **Outcome: performance raw score** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level n adjBeta (CI) continuous NR -0.81 n/a Stat Method: linear regression analysis **Outcome: processing speed raw score** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level n adjBeta (CI) continuous NR -0.93 n/a Stat Method: linear regression analysis **Outcome: verbal raw score** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level n adjBeta (CI) continuous NR -0.16 n/a Stat Method: linear regression analysis
Wasserman et al. (2011)	**Exposure Surrogate:** blood **Exposure Description:** venous whole	**Outcome: general intellectual ability (full-scale IQ)** ***blood arsenic concentration, µg/L*** Exp. Level n adjBeta (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cross-sectional **Location:** Bangladesh (Araihazar) **Population:** children 8-11 years old living in households within the HEALS cohort of villages n cases: n/a n control: n/a	blood samples collected at a field clinic and analyzed for Pb, Mn, Se, and As **Population-Level Exposure:** 4.81 µg/L mean 3.22SD	continuous NR -3.8 n/a Stat Method: linear regression **Outcome: perceptual reasoning** ***blood arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -1.13 n/a Stat Method: linear regression **Outcome: processing speed** ***blood arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.27 n/a Stat Method: linear regression **Outcome: verbal comprehension** ***blood arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -1.49 n/a Stat Method: linear regression **Outcome: working memory** ***blood arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.91 n/a Stat Method: linear regression
Wright et al. (2006) **Study Type:** cross-sectional **Location:** United States (OK) **Population:** school-age children residing near hazardous waste site n cases: n/a n control: n/a	**Exposure Surrogate:** hair **Exposure Description:** hair samples cleaned by sonication, rinsed and dried **Population-Level Exposure:** not available	**Outcome: CELF-3** ***hair arsenic levels, ppb*** no significant association between any CELF-3 test scores and hair As levels **Outcome: children's category test** ***hair arsenic levels, ppb*** no significant association between children's category test scores and hair As levels **Outcome: CVLT-C: list A** ***hair arsenic levels, ppb*** Exp. Level n adjBeta (CI) continuous NR -0.26 n/a Stat Method: unspecified **Outcome: CVLT-C: other than list A**

Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental		
Reference and Study Design	**Exposure Measures**	**Results**
		hair arsenic levels, ppb no significant association between any CVLT-C other than list A test scores and hair As levels; significant Mn-by-As interaction for scores
		Outcome: full-Scale IQ
		hair arsenic levels, ppb Exp. Level n adjBeta (CI) continuous NR -0.44 n/a Stat Method: mutivariate linear regression
		Outcome: parent ratings of children on CADS-IV, BRIEF tests
		hair arsenic levels, ppb no significant association between parent rating and arsenic
		Outcome: performance IQ
		hair arsenic levels, ppb Exp. Level n adjBeta (CI) continuous NR -0.27 n/a Stat Method: scatterplot slope
		Outcome: teacher ratings of children on CADS-IV, BRIEF, BASC tests
		hair arsenic levels, ppb no significant association between teacher rating and arsenic
		Outcome: verbal IQ
		hair arsenic levels, ppb Exp. Level n adjBeta (CI) continuous NR -0.51 n/a Stat Method: mutivariate linear regression
		Outcome: WRAML
		hair arsenic levels, ppb no significant association between any WRAML test scores and hair As levels; significant Mn-by-As interaction for scores on WRAML story memory
		Outcome: WRAVMA
		hair arsenic levels, ppb no significant association between any WRAVMA test scores and hair As levels

--: not reported; n: number of cases (when presented in Results column)

5.4.1 References Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental

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5.5 Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Amaral et al. (2012) **Study Type:** case-control **Location:** Spain (Mediterranean coast) **Population:** PANKRAS II Study 1992-1995, adults participants with exocrine pancreatic cancer n cases: 118 n control: 399	**Exposure Surrogate:** toenails **Exposure Description:** toenail arsenic concentration measured from clean samples **Population-Level Exposure:** 0-0.75 µg/g range	**Outcome: exocrine pancreatic cancer** ***toenail arsenic concentration (quartiles), µg/g*** Exp. Level / n / adjOR / (CI) ≤ 0.0518 / 34 / 1 / n/a 0.0519-0.0709 / 21 / 0.81 / n/a 0.0710-0.1061 / 23 / 1.22 / n/a >0.1061 / 35 / 2.02 / n/a Stat Method: logistic regression
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults) n exposed: 56,378 n total: 57,053	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** not available	**Outcome: colorectal cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 0.98 / 0.96, 1.01 Stat Method: Cox regression
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined	**Outcome: colorectal cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 0.97 / 0.90, 1.05 Stat Method: Cox regression

Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** 0.7 µg/L median	
Farzan et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (NH) **Population:** 4 month old infants born to pregnant women 18-45 years old in New Hampshire, USA n total: 214	**Exposure Surrogate:** urine **Exposure Description:** mothers provided spot urine sample upon enrollment (24-28 weeks gestation); samples that registered below the detection limit assigned a value equal to the detection limit divided by the square root of two; total urinary As calculated as the sum of inorganic As (As[III] and As[V]) and metabolic products MMA(V) and DMA(V), excluding arsenobetaine **Population-Level Exposure:** 6 µg/L mean 7.5SD	**Outcome: acute gastrointestinal symptoms, conditions, illnesses** ***maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L*** Exp. Level / n / RR / (CI) continuous: at least one infection / 21 / 1.2 / 1.7, 2.0 continuous: infection lasting 2 or more days / 10 / 1.9 / 0.9, 3.9 continuous: infection with a physician visit / 6 / 3.5 / 0.8, 15.4 continuous: infection treated with prescription medication / 1 / NR / n/a Stat Method: logistic regression
García-Esquinas et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	**Exposure Surrogate:** urine **Exposure Description:** individual urine samples collected and analyzed for arsenic speciation **Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	**Outcome: colon and rectal cancer** ***urinary arsenic concentration, µg/g-creatinine*** no significant association between arsenic and colon or rectal cancer **Outcome: esophagus and stomach cancer** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th percentiles / NR / 1.09 / 0.45, 2.66 Stat Method: Cox proportional hazard models; log transformed

Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Hsu et al. (2013b) **Study Type:** cohort (prospective) **Location:** Taiwan (SW: Peimen, Hsuechia, Ichu, and Putai Townships; NE: Chiaohsi, Chuangwei, Wuchieh, and Tungshan Townships) **Population:** residents of an arseniasis-endemic area with and without skin lesions n total: 9,525	**Exposure Surrogate:** drinking water **Exposure Description:** SW population: median arsenic level of several wells shared in a village derived from two surveys; NE population: arsenic level of well water samples collected during home interviews **Population-Level Exposure:** 10-500 µg/L range	**Outcome: colon cancer** ***arsenic concentration in well water (non-diabetes mellitus vs. diabetes mellitus subjects), µg/L*** Exp. Level / n / HR / (CI) non-DM w/ As <500 — NR — 1 — n/a DM w/ As <500 — NR — 1.6 — 1.00, 2.57 non-DM w/ As ≥ 500 — NR — 1 — n/a DM w/ As ≥ 500 — NR — 2.09 — 1.41, 9.14 Stat Method: Cox regression analysis **Outcome: rectal cancer** ***arsenic concentration in well water (non-diabetes mellitus vs. diabetes mellitus subjects), µg/L*** Exp. Level / n / HR / (CI) non-DM w/ As <500 — NR — 1 — n/a DM w/ As <500 — NR — 1.75 — 1.01, 3.05 non-DM w/ As ≥ 500 — NR — 1 — n/a DM w/ As ≥ 500 — NR — 1.34 — 0.35, 5.04 Stat Method: Cox regression analysis
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2,203 n total: 2,203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: digestive organs and peritoneum cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 — NR — 1.11 — n/a 1,000-4,999 — NR — 0.2 — n/a ≥ 5,000 — NR — 0.7 — n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 — NR — 0.57 — n/a 1,000-4,999 — NR — 0.87 — n/a ≥ 5,000 — NR — 0.73 — n/a Stat Method: standardized mortality ratios

Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: large intestine cancer ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 NR 1.23 n/a 1,000-4,999 NR NR n/a ≥ 5,000 NR 0.91 n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 NR 0.79 n/a 1,000-4,999 NR 0.45 n/a ≥ 5,000 NR 0.35 n/a Stat Method: standardized mortality ratios **Outcome: stomach cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 NR 1 n/a 1,000-4,999 NR 0.4 n/a ≥ 5,000 NR 0.7 n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 NR 0.67 n/a 1,000-4,999 NR 0.85 n/a ≥ 5,000 NR 1.2 n/a Stat Method: standardized mortality ratios
Rahman et al. (2011) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** MINIMat Study, mother-infant pairs n total: 1,552	**Exposure Surrogate:** maternal urine **Exposure Description:** maternal urinary arsenic concentration measured from urine samples collected at gestation weeks 8 and 30; arsenic exposure calculated as sum of inorganic arsenic and its methylated metabolites (MMA and DMA) and the average of exposure at gestation weeks 8 and 30; samples <LOD reanalyzed using larger volume; groups are quintiles **Population-Level Exposure:** 159 µg/L mean 163SD	**Outcome: diarrhea** ***maternal urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjRR / (CI) <39 NR 1 n/a 39-64 NR 0.99 0.83, 1.19 65-132 NR 0.96 0.80, 1.15 133-261 NR 1.25 1.05, 1.48 ≥ 261 NR 1.2 1.01, 1.43 Stat Method: Poisson regression

Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Sawada et al. (2013) **Study Type:** cohort (prospective) **Location:** Japan (Iwate, Akita, Nagano, Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90,378	**Exposure Surrogate:** diet **Exposure Description:** detailed questionnaire on food intake/frequency; average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	**Outcome: colorectal cancer** ***arsenic concentration in diet, µg/day*** arsenic not significantly associated with colorectal cancer **Outcome: stomach cancer** ***inorganic arsenic intake (females; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.6 / 65 / 1 / n/a 53.7 / 61 / 0.82 / 0.57, 1.16 62.6 / 74 / 0.93 / 0.66, 1.3 105.7 / 73 / 0.92 / 0.65, 1.29 Stat Method: Multivariate regression ***inorganic arsenic intake (males; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.5 / 164 / 1 / n/a 54.7 / 188 / 1.02 / 0.83, 1.26 63.5 / 166 / 0.88 / 0.7, 1.1 99.1 / 168 / 0.89 / 0.71, 1.11 Stat Method: Multivariate regression
Syed et al. (2013) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study, adult participants n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from single spot sample for each individual **Population-Level Exposure:** 7-5,000 µg/g-creatinine range	**Outcome: lesions of the gums** ***urinary arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) 7-134.0 / NR / 1 / n/a 134.1-286.0 / NR / 2.01 / 0.75, 5.4 286.1-5,000 / NR / 2.9 / 1.11, 7.54 Stat Method: multinomial multivariate regression **Outcome: lesions of the lips** ***urinary arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) 7-134.0 / NR / 1 / n/a 134.1-286.0 / NR / 2.34 / 0.60, 10.63 286.1-5,000 / NR / 2.68 / 0.67, 4.24 Stat Method: multinomial multivariate regression **Outcome: lesions of the tongue**

Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		urinary arsenic concentration (tertiles), µg/g-creatinine Exp. Level / n / adjOR / (CI) 7-134.0 / NR / 1 / n/a 134.1-286.0 / NR / 1.61 / 0.84, 3.08 286.1-5,000 / NR / 2.79 / 1.51, 5.15 Stat Method: multinomial multivariate regression
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho) **Population:** adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	**Outcome: colon cancer** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 / 2 / 2.98 / 0.53, 10.89 0.05-0.99 / 0 / 0 / 0, 22.14 ≥ 1 / 0 / 0 / 0, 17.11 Stat Method: Cox proportional hazard

--: not reported; n: number of cases (when presented in Results column)

5.5.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Digestive System Effects

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5.6 Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine system effects including Diabetes

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Chen et al. (2012a) **Study Type:** cohort (prospective) **Location:** Taiwan (Putai) **Population:** subjects from community-based cohort from an arseniasis endemic area with a high prevalence of black foot disease n exposed: 111 n reference: 136 n total: 247	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure defined as the sum of the products, derived by multiplying the arsenic concentration in well water by the duration of water consumption during consecutive periods of living at different villages **Population-Level Exposure:** 700-930 mg/L - yr range	**Outcome: metabolic syndrome (MetS)** ***cumulative arsenic exposure (CAE), mg/L - yr*** Exp. Level / n / adjOR / (CI) <12.6 / NR / 1 / n/a 12.6-18.9 / NR / 1.01 / 0.48, 1.89 >18.9 / NR / 1.73 / 0.72, 4.19 Stat Method: multiple logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** information on artesian well water usage collected for each participant **Population-Level Exposure:** 700-930 µg/L range	**Outcome: metabolic syndrome (MetS)** ***well water arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) <700 / NR / 1 / n/a 700-767.65 / NR / 1.25 / 0.66, 2.39 >767.65 / NR / 1.24 / 0.65, 2.37 Stat Method: multiple logistic regression ***well water arsenic concentration by metabolic syndrome status, µg/L*** Exp. Level / n / mean / (CI) no MetS / NR / 569.94 / n/a with MetS / NR / 684.39 / n/a Stat Method: Student's t-test
Chen et al. (2010c) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar)	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic TWA concentration calculated from well water samples for a set of 5,966 contiguous wells in the area based on drinking duration; subjects grouped for analysis in quintiles	**Outcome: diabetes** ***drinking water arsenic level (TWA): Model 1 (full population) (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) 0.1-8.0 / NR / 1 / n/a 8.1-41.0 / NR / 1.28 / .85, 1.91 41.2-91.7 / NR / 1.2 / .80, 1.81 91.8-176.1 / NR / 0.95 / .61, 1.47

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Population: Health Effects of Arsenic Longitudinal Study, adult participants n cases: 11,319 n control: n/a	**Population-Level Exposure:** 0.1-864 µg/L range	176.2-864.0 NR 1.08 .71, 1.65 Stat Method: Unconditional logistic regress
		drinking water arsenic level (TWA): Model 2 (BMI <20) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 NR 1 n/a 8.1-41.0 NR 1.74 .86, 3.49 41.2-91.7 NR 1.35 .65, 2.79 91.8-176.1 NR 0.83 .37, 1.87 176.2-864.0 NR 0.66 .28, 1.56 Stat Method: Unconditional logistic regression
		drinking water arsenic level (TWA): Model 2 (BMI ≥ 20) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 NR 1 n/a 8.1-41.0 NR 1.02 .63, 1.67 41.2-91.7 NR 1.01 .62, 1.65 91.8-176.1 NR 0.86 .51, 1.42 176.2-864.0 NR 1.13 .70, 1.82 Stat Method: Unconditional logistic regression
		drinking water arsenic level (TWA): Model 2 (full population) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 0.1-8.0 NR 1 n/a 8.1-41.0 NR 1.35 .9, 2.02 41.2-91.7 NR 1.24 .82, 1.87 91.8-176.1 NR 0.96 0.62, 1.49 176.2-864.0 NR 1.11 .73, 1.69 Stat Method: Unconditional logistic regression
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic concentration measured from single baseline sample for each individual **Population-Level Exposure:** 1-205 µg/L range	**Outcome: diabetes**
		urinary arsenic concentration: Model 1 (full population) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 1-36 NR 1 n/a 37-66 NR 1.29 0.87, 1.91 67-114 NR 0.99 0.65, 1.50 115-204 NR 0.9 0.59, 1.39 ≥ 205 NR 0.87 0.56, 1.36

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: Unconditional logistic regression
		urinary arsenic concentration: Model 2 (BMI <20 only) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.53 / .75, 3.12 67-114 / NR / 1.11 / .52, 2.34 115-204 / NR / 0.51 / .20, 1.27 ≥ 205 / NR / 0.7 / .30, 1.60 Stat Method: Unconditional logistic regression
		urinary arsenic concentration: Model 2 (BMI ≥ 20 only) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.16 / .72, 1.87 67-114 / NR / 1.01 / .61, 1.68 115-204 / NR / 1.14 / .7, 1.87 ≥ 205 / NR / 1.06 / .62, 1.8 Stat Method: Unconditional logistic regression
		urinary arsenic concentration: Model 2 (full population) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.29 / .87, 1.91 67-114 / NR / 1.05 / .69, 1.59 115-204 / NR / 0.94 / .61, 1.44 ≥ 205 / NR / 0.93 / .59, 1.45 Stat Method: Unconditional logistic regression
		urinary arsenic concentration: Model 3 (BMI <20 only) (quintiles), µg/L Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.62 / .79, 3.34 67-114 / NR / 1.23 / .56, 2.69 115-204 / NR / 0.59 / .22, 1.55 ≥ 205 / NR / 0.87 / .34, 2.25 Stat Method: Unconditional logistic

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		regression ***urinary arsenic concentration: Model 3 (BMI ≥ 20 only) (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.35 / .83, 2.21 67-114 / NR / 1.17 / .69, 1.98 115-204 / NR / 1.46 / .85, 2.51 ≥ 205 / NR / 1.41 / .77, 2.59 Stat Method: Unconditional logistic regression ***urinary arsenic concentration: Model 3 (full population) (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) 1-36 / NR / 1 / n/a 37-66 / NR / 1.44 / .97, 2.17 67-114 / NR / 1.2 / .77, 1.85 115-204 / NR / 1.16 / .73, 1.85 ≥ 205 / NR / 1.22 / .73, 2.03 Stat Method: Unconditional logistic regression
Chen et al. (2011a) **Study Type:** cross-sectional **Location:** Taiwan (Changhua County (central Taiwan)) **Population:** adult residents of village with history of higher than average arsenic in drinking water n cases: 910 n control: 133	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from spot sample for each individual; results below LOD assigned one-half of LOD **Population-Level Exposure:** 85.13 µg/g-creatinine median	**Outcome: diabetes mellitus** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) =<35 / NR / 1 / n/a >35-75 / NR / 1.95 / 0.56, 2.66 >75-200 / NR / 2.08 / 1.05, 3.69 >200 / NR / 2.22 / 1.21, 4.09 Stat Method: Multivariate logistic regression
Coronado-González et al. (2007)	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic	**Outcome: Type 2 diabetes mellitus** ***urinary arsenic concentration (50 µg/g cutoff tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: case-control **Location:** Mexico (Coahuila) **Population:** adult residents of arseniasis-endemic region n cases: 200 n control: 200	concentration measured from spot sample for each individual; subjects grouped for analysis in tertiles **Population-Level Exposure:** 35-104 µg/g-creatinine range	<50 NR 1 n/a 50-100 NR 1.41 0.57, 3.47 >100 NR 2.35 0.94, 5.91 Stat Method: multivariate analysis model with unconditional logistic regression ***urinary arsenic concentration (ACGIH cutoff tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <35 NR 1 n/a 35-100 NR 1.58 0.83, 3.02 >100 NR 2.45 1.27, 4.73 Stat Method: multivariate analysis model with unconditional logistic regression ***urinary arsenic concentration (tertiles in controls), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <63.5 NR 1 n/a 63.5-104 NR 2.16 1.23, 3.79 >104 NR 2.84 1.64, 4.92 Stat Method: multivariate analysis model with unconditional logistic regression ***urinary arsenic concentration (50 µg/g cutoff tertiles), µg/g-creatinine*** Exp. Level / n / OR / (CI) <50 NR 1 n/a 50-100 NR 1.56 0.81, 3.03 >100 NR 2.45 1.27, 4.80 Stat Method: multivariate analysis model with unconditional logistic regression ***urinary arsenic concentration (ACGIH cutoff tertiles), µg/g-creatinine*** Exp. Level / n / OR / (CI) <35 NR 1 n/a 35-100 NR 1.12 0.44, 2.97 >100 NR 1.95 0.75, 5.20 Stat Method: multivariate analysis model with unconditional logistic regression ***urinary arsenic concentration (tertiles in controls), µg/g-creatinine*** Exp. Level / n / OR / (CI) <63.5 NR 1 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		63.5-104 NR 1.94 1.11, 3.41 >104 NR 2.65 1.54, 4.58 Stat Method: multivariate analysis model with unconditional logistic regression
Del Razo et al. (2011) **Study Type:** cross-sectional **Location:** Mexico (Zimapan and Lagunera) **Population:** residents of arsenicosis-endemic areas of Mexico n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** each subject provided a sample of water used for drinking; cumulative exposure estimated from measurements of current and historical concentrations of inorganic arsenic in drinking water and duration of exposure; estimates generated for 1993-2008 period and for 5-year segments 1993-1997, 1998-2002, and 2003-2007 **Population-Level Exposure:** 0-6.73 ppm-years range	**Outcome: diabetes mellitus** ***cumulative inorganic arsenic exposure concentration in drinking water, ppm-years*** Exp. Level n adjOR (CI) cumulative exposure 1993-2008 NR 1.03 0.77, 1.39 cumulative exposure 2003-2007 NR 3.57 0.9, 14.19 cumulative exposure 1998-2002 NR 0.98 0.41, 2.37 cumulative exposure 1993-1997 NR 0.88 0.52, 1.48 Stat Method: logistical regression
	Exposure Surrogate: drinking water **Exposure Description:** each subject provided a sample of water used for drinking; mean inorganic arsenic concentrations in drinking water: 77.3 and 39.2 for diabetic and non-diabetic subpopulations, respectively **Population-Level Exposure:** 3.1-215.2 ppb range	**Outcome: diabetes mellitus** ***concentration of inorganic arsenic in drinking water, ppb*** Exp. Level n adjOR (CI) current concentration NR 1.13 1.05, 1.22 NR NR NR n/a Stat Method: logistical regression **Outcome: fasting plasma insulin (FPI)** ***concentration of inorganic arsenic in drinking water (log-transformed), ppb*** Exp. Level n adjBeta (CI) continuous NR -2.084 -2.72, -1.448 Stat Method: linear regression, with log-transformation **Outcome: homeostatic model assessment - insulin resistance (HOMA-IR)** ***concentration of inorganic arsenic in drinking water (log-transformed), ppb***

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjBeta / (CI) continuous / NR / -1.641 / -2.358, -0.924 Stat Method: linear regression, with log-transformation
	Exposure Surrogate: urine **Exposure Description:** spot urine sample collected from each subject during the medical exam; concentrations of inorganic arsenic and methylated metabolites measured to assess inorganic arsenic metabolism **Population-Level Exposure:** 2.3-233.7 ng/mL range	**Outcome: diabetes mellitus** ***urinary total arsenic concentration, ng/mL*** Exp. Level / n / adjOR / (CI) urinary tAs / NR / 1.12 / 0.78, 1.62 Stat Method: logistic regression
		Outcome: fasting plasma insulin (FPI) ***urinary total arsenic concentration (log-transformed), ng/mL*** Exp. Level / n / adjBeta / (CI) continuous / NR / -5.313 / -8.068, -2.559 Stat Method: linear regression, with log-transformation
		Outcome: homeostatic model assessment - insulin resistance (HOMA-IR) ***urinary total arsenic concentration (log-transformed), ng/mL*** Exp. Level / n / adjBeta / (CI) continuous / NR / -4.538 / -7.514, -1.562 Stat Method: linear regression, with log-transformation
Ettinger et al. (2009) **Study Type:** cohort (prospective) **Location:** United States (Tar Creek Superfund site, Ottawa County, OK) **Population:** pregnant women living near Superfund site n exposed: 399	**Exposure Surrogate:** blood **Exposure Description:** whole-blood arsenic concentration determined from blood samples collected at delivery; grouped for analysis in quartiles **Population-Level Exposure:** 1.7 µg/L geo mean 1.5SD	**Outcome: impaired glucose tolerance** ***blood arsenic concentration (IQR), µg/L*** Exp. Level / n / adjOR / (CI) 1.2 / NR / 1.65 / 0.521.52, 1.79 Stat Method: Multivariate logistic regression
		blood arsenic concentration (quartile), µg/L Exp. Level / n / adjOR / (CI) 0.23-0.92 / NR / 1 / n/a 0.93-1.39 / NR / 1.02 / 0.39, 2.69 1.4-2.08 / NR / 2.65 / 1.12, 6.36 2.09-24.07 / NR / 2.79 / 1.13, 6.87 Stat Method: Multivariate logistic regression
	Exposure Surrogate: hair	**Outcome: impaired glucose tolerance** ***hair arsenic concentration (IQR), ng/g***

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
n reference: 133 n total: 532	**Exposure Description:** hair arsenic concentration determined from hair samples collected at delivery from population subset with chemically untreated hair; grouped for analysis in quartiles **Population-Level Exposure:** 27.4 ng/g geo mean	Exp. Level / n / adjOR / (CI) 15.3 / NR / 2.32 / 0.52, 10.39 Stat Method: Multivariate logistic regression ***hair arsenic concentration (quartile), ng/g*** Exp. Level / n / adjOR / (CI) 1.1-8.81 / NR / 1 / n/a 8.93-13.11 / NR / 3.97 / 0.62, 25.37 13.26-24.12 / NR / 5.77 / 0.98, 33.88 24.22-724.41 / NR / 4.2 / 0.74, 23.86 Stat Method: Multivariate logistic regression
García-Esquinas et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	**Exposure Surrogate:** urine **Exposure Description:** individual urine samples collected and analyzed for arsenic speciation **Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	**Outcome: pancreatic cancer** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th percentiles / 25 / 2.46 / 1.09, 5.58 Stat Method: Cox proportional hazard models; log transformed
Gribble et al. (2012) **Study Type:** cross-sectional **Location:** United States (Arizona; Oklahoma; North Dakota; South Dakota) **Population:** Strong Heart Study, adults with stored urine samples available n cases: 2,954 n control: 971	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from spot sample for each individual; subjects grouped for analysis in quartiles **Population-Level Exposure:** 14.1 µg/L median, 7.9-24.2 µg/L 25th percentile	**Outcome: diabetes** ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjPR / (CI) 25th percentile / NR / 1 / n/a 75th percentile / NR / 1.14 / 1.08, 1.20 Stat Method: Poisson regression models ***urinary arsenic concentration (quartiles), µg/L*** Exp. Level / n / adjPR / (CI) <7.9 / 413 / 1 / n/a 7.9 - 14.1 / 492 / 1.15 / 1.04, 1.27 14.1 - 24.2 / 503 / 1.21 / 1.08, 1.34 >24.2 / 531 / 1.28 / 1.14, 1.44 Stat Method: Poisson regression models
Guo et al. (2007)	**Exposure Surrogate:** drinking water	**Outcome: glucosuria**

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cross-sectional **Location:** Mongolia region not available **Population:** residents of villages in the Hetao Plain, Inner Mongolia n cases: 680 n control: 189	**Exposure Description:** arsenic samples from 94 water sources, including wells; arsenic exposure determined by location of village **Population-Level Exposure:** 50-1,860 µg/L range	***water arsenic concentration, µg/L*** arsenic not significantly associated with glucosuria
Hsieh et al. (2008a) **Study Type:** case-control (nested) **Location:** Taiwan (Lanyang Basin (arsenic-exposed population)) **Population:** adult male residents of Taiwan from existing cohort n cases: 129 n control: 48	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentrations determined from well water samples collected during home interview **Population-Level Exposure:** 0.15-3,590 ppb range	**Outcome: free testosterone (nmol/L)** ***drinking water arsenic concentration, ppb*** Exp. Level / n / mean / (CI) ≤ 50 / NR / 0.38 / n/a >50 / NR / 0.31 / n/a Stat Method: ANOVA **Outcome: sex hormone-binding globulin (SHBG) (nmol/L)** ***drinking water arsenic concentration, ppb*** average level of SHBG not significantly different between subjects with or without arsenic exposure **Outcome: testosterone (nmol/L)** ***drinking water arsenic concentration, ppb*** Exp. Level / n / mean / (CI) ≤ 50 / NR / 17.55 / n/a >50 / NR / 15.04 / n/a Stat Method: ANOVA
Hsu et al. (2013b) **Study Type:** cohort (prospective) **Location:** Taiwan (SW: Peimen, Hsuechia, Ichu, and Putai Townships;	**Exposure Surrogate:** drinking water **Exposure Description:** SW population: median arsenic level of several wells shared in a village derived from two surveys; NE population: arsenic level of well water samples collected during home interviews	**Outcome: diabetes mellitus (DM)** ***arsenic concentration in well water, µg/L*** Exp. Level / n / Prev / (CI) <10 / 774 / 30.8 / n/a 10-49.9 / 505 / 26.4 / n/a 50-99.9 / 217 / 25.8 / n/a 100-499.9 / 397 / 31 / n/a ≥ 500 / 520 / 43.4 / n/a missing / 595 / 33.3 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
NE: Chiaohsi, Chuangwei, Wuchieh, and Tungshan Townships) **Population:** residents of an arseniasis-endemic area with and without skin lesions n total: 9,525	**Population-Level Exposure:** 10-500 µg/L range	Stat Method: not reported **Outcome: pancreatic cancer** ***arsenic concentration in well water (non-diabetes mellitus vs. diabetes mellitus subjects), µg/L*** Exp. Level / n / HR / (CI) non-DM w/ As <500 / NR / 1 / n/a DM w/ As <500 / NR / 3.03 / 1.22, 7.55 non-DM w/ As ≥ 500 / NR / 1 / n/a DM w/ As ≥ 500 / NR / 1.86 / 0.38, 9.02 Stat Method: Cox regression analysis
Islam et al. (2012b) **Study Type:** cross-sectional **Location:** Bangladesh (Kandirpar, Gobindogonj, Uttarda, Modaffargonj, Jolmuttar, Sunorpur, Durgapur) **Population:** adults living in unions of high arsenic contamination n cases: 89 n control: 915	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated by multiplying arsenic concentration of single tube well measurement for each individual with self-reported duration of use; subjects grouped for analysis above and below maximum acceptable limit in drinking water in Bangladesh (50 µg/L) and as quartiles **Population-Level Exposure:** 159 µg/L mean 198.5SD	**Outcome: type 2 diabetes** ***cumulative drinking water arsenic exposure, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 50 / NR / 1 / n/a >50 / NR / 2.1 / 1.3, 3.2 Stat Method: multivariate logistic regression ***cumulative drinking water arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) <22 / NR / 1 / n/a 23-32 / NR / 1.1 / 0.5, 2.3 33-261 / NR / 1.7 / 0.5, 3.2 ≥ 262 / NR / 1.9 / 1.1, 3.5 Stat Method: multivariate logistic regression
James et al. (2013) **Study Type:** case-cohort **Location:** United States (CO)	**Exposure Surrogate:** drinking water **Exposure Description:** residential water samples (both private well and public water) collected at time of interview (n=334); arsenic concentrations in the San Luis Valley ranged from non-detectable to 752 µg/L with a mean	**Outcome: diabetes mellitus (DM)** ***arsenic exposure TWA, per 15 µg/L*** Exp. Level / n / HR / (CI) per 15 µg/L increase in TWA arsenic / NR / 1.27 / 1.02, 1.64 Stat Method: Cox proportional hazards model ***arsenic exposure TWA, µg/L-year***

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Population: San Luis Valley Diabetes Study (SLVDS) participants with type II diabetes mellitus n cases: 141 n control: 347	concentration of 39 µg/L **Population-Level Exposure:** 39 µg/L-year mean, 0-752 µg/L-year range	Exp. Level / n / HR / (CI) 1 - <4 / NR / 1 / n/a 4 - <8 / NR / 1.11 / 0.82, 1.95 8 - <20 / NR / 1.42 / 0.94, 2.48 ≥ 20 / NR / 1.55 / 1.00, 2.51 Stat Method: Cox proportional hazards model
Jensen and Hansen (1998) **Study Type:** cross-sectional **Location:** Denmark region not available **Population:** occupationally exposed adult workers n cases: 40 n control: 26	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration determined from two urine samples collected from each individual **Population-Level Exposure:** 12-80 nmol/mmol creatinine range	**Outcome: HbA1c** ***urinary arsenic concentration, nmol/mmol creatinine*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.0078 / n/a Stat Method: multiple regression
Kim and Lee (2011) **Study Type:** cross-sectional **Location:** South Korea (national) **Population:** KNHANES IV 2008, adult participants n cases: 1,677 n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from single sample for each individual **Population-Level Exposure:** 118.4 µg/g-creatinine geo mean, 112.9-123.8 µg/g-creatinine 95% CI lower	**Outcome: diabetes mellitus** ***log-transformed total urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) continuous (females) / NR / 1.502 / 1.038, 2.171 continuous (males) / NR / 1.126 / 0.803, 1.577 Continuous (all) / NR / 1.312 / 1.040, 1.655 Stat Method: multiple logistic regression ***log-transformed total urinary arsenic - female, µg/g-creatinine*** Exp. Level / n / adjRR / (CI) diabetes - no / NR / 1 / n/a diabetes - yes / NR / 1.238 / 1.025, 1.494 Stat Method: multiple regression ***log-transformed total urinary arsenic - male,***

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		µg/g-creatinine Exp. Level / n / adjRR / (CI) diabetes - no / NR / 1 / n/a diabetes - yes / NR / 1.085 / 0.894, 1.316 Stat Method: multiple regression
		log-transformed total urinary arsenic - comb sex, µg/g-creatinine Exp. Level / n / adjRR / (CI) diabetes - no / NR / 1 / n/a diabetes - yes / NR / 1.154 / 1.014, 1.314 Stat Method: multiple regression
Kim et al. (2013) **Study Type:** case-control (nested) **Location:** United States (Arizona) **Population:** longitudinal study participants who developed diabetes within 10 years of initial screening n cases: 150 n control: 150	**Exposure Surrogate:** urine **Exposure Description:** concentrations of arsenic (total and inorganic) and metabolites measured in stored urine samples obtained at the baseline examination; adjusted for urinary creatinine **Population-Level Exposure:** 21.1 µg/L median, 15.3-29.4 µg/L 25th percentile	**Outcome: mean 2-hour postload plasma glucose** ***total arsenic concentration, µg/L*** 2-hour postload plasma glucose was correlated negatively with MMA and %MMA; correlations only changed slightly when adjusted for potential confounders **Outcome: mean fasting plasma glucose** ***total arsenic concentration, µg/L*** fasting plasma glucose was correlated negatively with %MMA and positively with total arsenic, inorganic arsenic, and DMA; correlations only changed slightly when adjusted for potential confounders **Outcome: type 2 diabetes (Model 3)** ***inorganic arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) continuous / 150 / 1.16 / 0.89, 1.53 Stat Method: logistic regression ***inorganic arsenic concentration (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) quartile 1 / NR / 1 / n/a quartiles 2-4 / NR / 2.14 / 1.19, 3.85 Stat Method: logistic regression ***total arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) continuous / 150 / 1.11 / 0.79, 1.57

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: logistic regression
Lai et al. (1994) **Study Type:** cross-sectional **Location:** Taiwan (Homei, Fuhsin, and Hsinming villages (Putai Township)) **Population:** adults living in arseniasis-endemic township n cases: 610 n control: 108	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated as the drinking water arsenic concentration multiplied by self-reported years living in a particular village and added across individual's lifetime; arsenic levels in well water collected in previous studies conducted in the 1960s; exposure not calculated for 19.4% due to lack of arsenic measurements in areas outside endemic area **Population-Level Exposure:** 0-15.1 ppm-years range	**Outcome: diabetes mellitus** ***Duration of drinking artesian well water (years), ppm-years*** Exp. Level / n / adjOR / (CI) 0 years / NR / 1 / n/a 1-10 years / NR / 1.3 / , 11-20 years / NR / 1.5 / , ≥ 21 years / NR / 1.9 / , Stat Method: Mantel-Haenszel chi-square test ***cumulative drinking water arsenic exposure, ppm-years*** Exp. Level / n / adjOR / (CI) 0 / NR / 1 / n/a 0.1-15.0 / NR / 6.61 / 0.86, 51.0 ≥ 15.1 / NR / 10.05 / 1.30, 77.9 Unknown / NR / 5.69 / 0.71, 45.5 Stat Method: multivariate logistic regression
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2,203 n total: 2,203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: diabetes mellitus** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 1.14 / n/a 1,000-4,999 / NR / 1.72 / n/a ≥ 5,000 / NR / 0.89 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 0.93 / n/a 1,000-4,999 / NR / 0.95 / n/a ≥ 5,000 / NR / 0.42 / n/a Stat Method: standardized mortality ratios **Outcome: pancreatic cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / NR / n/a 1,000-4,999 / NR / 0.35 / n/a ≥ 5,000 / NR / 0.31 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 0.21 / n/a 1,000-4,999 / NR / 1.44 / n/a ≥ 5,000 / NR / 0.86 / n/a Stat Method: standardized mortality ratios
Li et al. (2013a) **Study Type:** cross-sectional **Location:** China (Tuoketuo County, Inner Mongolia) **Population:** residents exposed to arsenic in drinking water n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration of each tube well measured and provided by local public health government; cumulative arsenic exposure (CAE) calculated for each subject as: concentration in tube well that subject used in his/her residential duration multiplied by duration of water consumption **Population-Level Exposure:** 0-760 µg/L range	**Outcome: type 2 diabetes (T2D)** ***water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <10 / NR / NR / n/a 10-50 / NR / 1.362 / 0.519, 3.571 >50 / NR / 1.578 / 0.584, 4.262 Stat Method: multiple logistic regression
Navas-Acien et al. (2008) **Study Type:** cross-sectional **Location:** United States region not available **Population:** NHANES 2003-2008, adult participants who had fasted before venipuncture n cases: 788 n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from spot sample for each individual; subjects grouped for analysis in tertiles **Population-Level Exposure:** 4.8-10.8 µg/L range	**Outcome: diabetes, type 2** ***urinary arsenic concentration*** ***, µg/L*** Exp. Level / n / adjOR / (CI) 20th percentile / NR / 1 / n/a 80th percentile / NR / 3.58 / 1.18, 10.83 Stat Method: logistic regression ***urinary arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) <4.8 / NR / 1 / n/a 4.8-10.8 / NR / 1.27 / 0.36, 4.48 >10.8 / NR / 1.6 / 0.46, 5.54 Stat Method: logistic regression
Navas-Acien et al.	**Exposure Surrogate:** urine	**Outcome: Type 2 diabetes**

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
(2009) **Study Type:** cross-sectional **Location:** United States region not available **Population:** NHANES 2003-2006, adult participants who had fasted before venipuncture n cases: n/a n control: n/a	**Exposure Description:** urinary arsenic concentration measured from spot sample for each individual **Population-Level Exposure:** 7.4 µg/L median	***urinary arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) 20th percentile / NR / 1 / n/a 80th percentile / NR / 2.86 / 1.23, 6.63 Stat Method: Statistical methods were conducted in a similar manner to Navas-Acien 2008
		urinary arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) ≤ 20th percentile / NR / 1 / n/a ≥ 80th percentile / NR / 1.78 / 0.6, 5.30 Stat Method: Statistical methods were conducted in a similar manner to Navas-Acien 2008
		urinary arsenic concentration in participants with undetectable (<0.4 µg/L) arsenobetaine, µg/L Exp. Level / n / adjOR / (CI) 20th percentile / NR / 1 / n/a 80th percentile / NR / 2.6 / 1.12, 6.03 Stat Method: Statistical methods were conducted in a similar manner to Navas-Acien 2008
		urinary arsenic concentration in participants with undetectable (<0.4 µg/L) arsenobetaine, µg/L Exp. Level / n / adjOR / (CI) ≤ 20th percentile / NR / 1 / n/a ≥ 80th percentile / NR / 4.26 / 0.83, 21.8 Stat Method: Statistical methods were conducted in a similar manner to Navas-Acien 2008
		urinary arsenic concentration minus arsenobetaine and arsenocholine, µg/L Exp. Level / n / adjOR / (CI) 20th / NR / 1 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		percentile 80th percentile NR 1.72 0.85, 3.45 Stat Method: Statistical methods were conducted in a similar manner to Navas-Acien 2008
		urinary arsenic concentration minus arsenobetaine and arsenocholine, µg/L Exp. Level / n / adjOR / (CI) ≤ 20th percentile NR 1 n/a ≥ 80th percentile NR 1.04 0.3, 3.59 Stat Method: Statistical methods were conducted in a similar manner to Navas-Acien 2008
Nizam et al. (2013) **Study Type:** case-control **Location:** Bangladesh (Faridpur District, 130 km southwest of Dhaka) **Population:** adults in arsenic-contaminated area with type II diabetes n cases: 140 n control: 180	**Exposure Surrogate:** urine **Exposure Description:** spot urine sample collected at time of recruitment; arsenic species measured; mean (95% CI) for absolute urinary inorganic arsenic was 20 (15.7-23.8) and 21.2 (17.9-24.5) for cases and controls, respectively **Population-Level Exposure:** 15.7-24.5 µg/L range	**Outcome: type 2 diabetes** ***urinary inorganic arsenic percent of total*** Exp. Level / n / mean / (CI) non-diabetic controls 0 10.5 n/a diabetic cases 140 9.5 n/a Stat Method: three-way analysis of variance with case-control and matching factors (sex and union) as the fixed factors
Pan et al. (2013) **Study Type:** case-control **Location:** Bangladesh region not available	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water collected for each individual from tube well identified as primary drinking water source; samples below LOD assigned value of 0.5 µg/L; average recovery of 95%	**Outcome: type 2 diabetes mellitus (T2DM)** ***arsenic concentration in drinking water (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) ≤ 1.7 11 1 n/a 1.8-15.5 19 1.92 0.84, 4.35 15.6-170.0 24 3.07 1.38, 6.85 ≥ 170.1 28 4.51 2.01, 10.09 Stat Method: logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Population: adults with type II diabetes mellitus and varying levels of arsenic exposure from drinking water n cases: 84 n control: 849	**Population-Level Exposure:** 1.7-170.1 µg/L range	
	Exposure Surrogate: toenails **Exposure Description:** toenail samples collected from each individual; concentrations corrected for systematic errors by normalizing sample concentration against measured average daily NIST arsenic concentration; average recovery of 86.5% **Population-Level Exposure:** 0.93-6.19 µg/g range	**Outcome: type 2 diabetes mellitus (T2DM)** ***arsenic concentration in toenail samples (quartiles), µg/g*** Exp. Level / n / adjOR / (CI) ≤ 0.93 / 10 / 1 / n/a 0.94-2.12 / 24 / 3.34 / 1.46, 7.64 2.13-6.18 / 22 / 3.4 / 1.46, 7.89 ≥ 6.19 / 28 / 6.22 / 2.63, 14.69 Stat Method: logistic regression
Rhee et al. (2013) **Study Type:** cross-sectional **Location:** Korea, Republic Of region not available **Population:** adults in Korea National Health and Nutrition Examination Survey (KNHANES) n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description: urine** samples collected after a fast of 8 hours; clean mid-stream urine collected for analysis; all samples had concentrations >LOD; inter-assay coefficients of variation for the urinary arsenic assay were 2.5-3.2% in 2008 and 2.3-4.3% in 2009 **Population-Level Exposure:** 70.7-193.4 µg/g-creatinine range	**Outcome: diabetes mellitus (DM)** ***urinary total arsenic concentration (quartiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) <70.7 / NR / 1 / n/a 70.7-117.7 / NR / 1.11 / 0.73, 1.68 117.7-<193.4 / NR / 1.42 / 0.94, 2.13 ≥ 193.4 / NR / 1.56 / 1.03, 2.36 Stat Method: logistic regression analysis **Outcome: glucose tolerance status** ***urinary total arsenic concentration, µg/g-creatinine*** arsenic not significantly associated with glucose tolerance **Outcome: insulin resistance (HOMA2%S)** ***urinary total arsenic concentration, µg/g-creatinine*** arsenic not significantly associated with HOMA2%S **Outcome: insulin secretion capacity (HOMA2%B)** ***urinary total arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.04 / n/a Stat Method: multivariate regression analysis
Sawada et al. (2013)	**Exposure Surrogate:** diet	**Outcome: pancreas cancer**

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cohort (prospective) **Location:** Japan (Iwate, Akita, Nagano, Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90,378	**Exposure Description:** detailed questionnaire on food intake/frequency; average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	***inorganic arsenic intake (females; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.6 / 20 / 1 / n/a 53.7 / 31 / 1.62 / 0.91, 2.88 62.6 / 27 / 1.38 / 0.76, 2.51 105.7 / 27 / 1.37 / 0.75, 2.49 Stat Method: Multivariate regression ***inorganic arsenic intake (males; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.5 / 34 / 1 / n/a 54.7 / 31 / 0.8 / 0.49, 1.32 63.5 / 46 / 1.14 / 0.72, 1.8 99.1 / 31 / 0.78 / 0.47, 1.29 Stat Method: Multivariate regression
Steinmaus et al. (2009) **Study Type:** cross-sectional **Location:** United States (National) **Population:** NHANES 2003-2004, adult participants who had fasted before venipuncture n cases: 795 n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from spot sample for each individual; subjects grouped for analysis in tertiles **Population-Level Exposure:** 16.7 µg/L mean 39.7SD	**Outcome: Type 2 diabetes mellitus** ***estimated inorganic urinary arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) ≤ 4.1 / NR / 1 / n/a 4.2-8.5 / NR / 0.63 / 0.34, 1.15 >8.5 / NR / 0.98 / 0.53, 1.80 Stat Method: Logistic regression with non-log transformed data ***urinary arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) =<20th (=<3.5) / NR / 1 / n/a ≥ 80th (≥ 18.3) / NR / 0.88 / 0.39, 1.97 Stat Method: Logistic regression with non-log transformed data ***urinary arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) =<5.2 / NR / 1 / n/a 5.3-11.8 / NR / 0.87 / 0.48, 1.55 >11.8 / NR / 0.76 / 0.42, 1.39 Stat Method: Logistic regression with non-log transformed data

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		estimated inorganic urinary arsenic concentration, µg/L Exp. Level / n / OR / (CI) =<20th (≤ 2.7) / NR / 1 / n/a ≥ 80th (≥ 11.9) / NR / 1.12 / 0.59, 2.15 Stat Method: Logistic regression with non-log transformed data
		estimated inorganic urinary arsenic concentration (tertiles), µg/L Exp. Level / n / OR / (CI) ≤ 4.1 / NR / 1 / n/a 4.2-8.5 / NR / 0.77 / 0.46, 1.30 >8.5 / NR / 0.9 / 0.54, 1.49 Stat Method: Logistic regression with non-log transformed data
		urinary arsenic concentration, µg/L Exp. Level / n / OR / (CI) =<20th (=<3.5) / NR / 1 / n/a ≥ 80th (≥ 18.3) / NR / 0.8 / 0.41, 1.59 Stat Method: Logistic regression with non-log transformed data
		urinary arsenic concentration (tertiles), µg/L Exp. Level / n / OR / (CI) =<5.2 / NR / 1 / n/a 5.3-11.8 / NR / 0.9 / 0.54, 1.49 >11.8 / NR / 0.82 / 0.49, 1.38 Stat Method: Logistic regression with non-log transformed data
		estimated inorganic urinary arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) =<20th (≤ 2.7) / NR / 1 / n/a ≥ 80th (≥ 11.9) / NR / 1.15 / 0.53, 2.50 Stat Method: Logistic regression with non-log transformed data; age, BMI, blood mercury, urinary creatinine, urinary albumin, and

Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects including Diabetes		
Reference and Study Design	**Exposure Measures**	**Results**
		serum cotinine were entered as continuous variables
Tseng et al. (2000) **Study Type:** cohort (prospective) **Location:** Taiwan (three villages on southwest coast) **Population:** adult residents of arseniasis-endemic villages n exposed: 446 n reference: Not reported n total: 446	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated based on arsenic concentration in well water and self-reported years of drinking well water during successive periods of living in different villages **Population-Level Exposure:** 17-17 mg/L x yr range	**Outcome: diabetes mellitus** ***cumulative drinking water arsenic exposure, mg/L x yr*** Exp. Level / n / adjRR / (CI) <17 / NR / 1 / n/a ≥ 17 / NR / 2.1 / 1.1, 4.2 Stat Method: Cox's proportional hazards model ***cumulative drinking water arsenic exposure, mg/L x yr*** Exp. Level / n / RR / (CI) <17 / NR / 1 / n/a ≥ 17 / NR / 2.5 / 1.4, 4.7 Stat Method: Cox's proportional hazards model

--: not reported; n: number of cases (when presented in Results column)

5.6.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Endocrine System Effects Including Diabetes

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5.7 Summary of Observational Epidemiology Studies for Health Effect Category: Hematology, Hematopoietic System

Summary of Observational Epidemiology Studies for Health Effect Category: Hematology, Hematopoietic System		
Reference and Study Design	**Exposure Measures**	**Results**
Del Razo et al. (2011) **Study Type:** cross-sectional **Location:** Mexico (Zimapan and Lagunera) **Population:** residents of arsenicosis-endemic areas of Mexico n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** each subject provided a sample of water used for drinking; mean inorganic arsenic concentrations in drinking water: 77.3 and 39.2 for diabetic and non-diabetic subpopulations, respectively **Population-Level Exposure:** 3.1-215.2 ppb range	**Outcome: HbA1c levels** ***concentration of inorganic arsenic in drinking water (log-transformed), ppb*** Exp. Level: continuous; n: NR; adjBeta: 0.193; (CI): 0.018, 0.369 Stat Method: linear regression, with log-transformation
	Exposure Surrogate: urine **Exposure Description:** spot urine sample collected from each subject during the medical exam; concentrations of inorganic arsenic and methylated metabolites measured to assess inorganic arsenic metabolism **Population-Level Exposure:** 2.3-233.7 ng/mL range	**Outcome: HbA1c levels** ***urinary total arsenic concentration (log-transformed), ng/mL*** Exp. Level: continuous; n: NR; adjBeta: 0.164; (CI): -0.57, 0.898 Stat Method: linear regression, with log-transformation
Guo et al. (2007) **Study Type:** cross-sectional **Location:** Mongolia **Population:** residents of villages in the Hetao Plain, Inner Mongolia n cases: 680 n control: 189	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic samples taken from 94 water sources, including wells; detection limit not specified, but authors note reliability of the method at <10 µg/L; arsenic exposure determined by location of village **Population-Level Exposure:** 50-1,860 µg/L range	**Outcome: anemia** ***water arsenic concentration, µg/L*** arsenic not significantly associated with anemia

Summary of Observational Epidemiology Studies for Health Effect Category: Hematology, Hematopoietic System		
Reference and Study Design	**Exposure Measures**	**Results**
Heck et al. (2008) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) cohort n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** time-weighted arsenic exposure calculated based on drinking water duration from each well as reported by participants and well concentration measured in samples; levels below detection reanalyzed using ICP-MS with lower detection limit; exposure groups split in to quartiles (quartile concentrations not provided for women) **Population-Level Exposure:** 0-200 µg/L range	**Outcome: hemoglobin** ***time-weighted well water arsenic concentration (all men), µg/L*** Exp. Level / n / mean / (CI) 0-<50 / NR / 13.9 / n/a 50-<100 / NR / 13.9 / n/a 100-<200 / NR / 13.9 / n/a >200 / NR / 13.8 / n/a Stat Method: generalized linear modeling ***time-weighted well water arsenic concentration quartiles (women with Hgb ≤ 10 g/dL), µg/L*** Exp. Level / n / mean / (CI) lowest quartile / NR / 8.2 / n/a 2nd quartile / NR / 7.2 / n/a 3rd quartile / NR / 7.1 / n/a highest quartile / NR / 6.4 / n/a Stat Method: generalized linear modeling
	Exposure Surrogate: urine **Exposure Description:** total urine arsenic level measured in spot urine samples **Population-Level Exposure:** 50-200 µg/L range	**Outcome: hemoglobin** ***urine arsenic level (all men), µg/L*** Exp. Level / n / mean / (CI) <50 / NR / 13.9 / n/a 50-99 / NR / 13.8 / n/a 100-199 / NR / 13.8 / n/a 200 / NR / 13.6 / n/a Stat Method: generalized linear modeling ***urine arsenic level (women with Hgb ≤ 10 g/dL), µg/L*** Exp. Level / n / mean / (CI) <50 / NR / 10.2 / n/a 50-99 / NR / 9.3 / n/a 100-199 / NR / 8 / n/a 200 / NR / 8.2 / n/a Stat Method: generalized linear modeling
Majumdar et al. (2009) **Study Type:** cross-sectional **Location:** India (West	**Exposure Surrogate:** drinking water **Exposure Description:** for each participant, water samples from private or public tube wells analyzed for arsenic; exposure categories developed based on	**Outcome: anaemia** ***arsenic concentration in drinking water (females), µg/L*** Exp. Level / n / prevOR / (CI) <50 / NR / 1 / n/a ≥ 500 / NR / 3.85 / 2.6, 5.5 Stat Method: prevalence odds ratio

Summary of Observational Epidemiology Studies for Health Effect Category: Hematology, Hematopoietic System		
Reference and Study Design	**Exposure Measures**	**Results**
Bengal) **Population:** residents of arsenic-affected villages with comparison population from low exposure area n cases: 3,825 n control: 3,451	arsenic levels **Population-Level Exposure:** 50-500 µg/L range	calculated for each outcome comparing highest and lowest exposure levels ***arsenic concentration in drinking water (males), µg/L*** Exp. Level / n / prevOR / (CI) <50 / NR / 1 / n/a ≥ 500 / NR / 2.41 / 1.3, 4.2 Stat Method: prevalence odds ratio calculated for each outcome comparing highest and lowest exposure levels

--: not reported; n: number of cases (when presented in Results column)

5.7.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Hematology, Hematopoietic System

Del Razo, LM; García-Vargas, GG; Valenzuela, OL; Castellanos, EH; Sánchez-Peña, LC; Currier, JM; Drobná, Z; Loomis, D; Stýblo, M. (2011). Exposure to arsenic in drinking water is associated with increased prevalence of diabetes: a cross-sectional study in the Zimapán and Lagunera regions in Mexico. Environ Health 10: 73. http://dx.doi.org/10.1186/1476-069X-10-73

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5.8 Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Ahmed et al. (2012) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** women and infants enrolled in MINIMat study of nutritional impact on fetal and infant development n total: 130	**Exposure Surrogate:** maternal blood **Exposure Description:** maternal blood samples collected at gestation week 14 analyzed for arsenic content **Population-Level Exposure:** 4.7 µg/kg median, 1.4-22.2 µg/kg 5th percentile	**Outcome: sjTRECs in cord blood** ***ln blood arsenic at gestation week 14, µg/kg*** Exp. Level / n / adjBeta / (CI) <1.8 / NR / -1.27 / -1.89, -0.66 ≥ 1.8 / NR / 0.7 / -0.01, 1.41 Stat Method: spline regression model using spline knots at ln blood arsenic 1.8
	Exposure Surrogate: urine **Exposure Description:** maternal urine samples taken at gestation week 8 or 30 analyzed for inorganic arsenic and metabolites; samples adjusted for specific gravity **Population-Level Exposure:** 69 µg/L median, 19-441 µg/L 5th percentile	**Outcome: sjTRECs in cord blood** ***ln urinary arsenic at gestation week 8, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.25 / -0.48, -0.01 Stat Method: linear regression ***ln urinary arsenic at gestation week 30, µg/L*** Exp. Level / n / adjBeta / (CI) <5 / NR / -0.53 / -0.93, -0.13 ≥ 5 / NR / 0.15 / -0.55, 0.85 Stat Method: spline regression model using spline knots at ln urinary arsenic 5.0
Biswas et al. (2008) **Study Type:** cross-sectional **Location:** India (Murshidabad district, West Bengal) **Population:** adult residents of area with high arsenic water concentrations with	**Exposure Surrogate:** level of exposure **Exposure Description:** adult residents of area with high arsenic water concentrations with arsenic induced skin lesions (individuals with arsenicosis); comparison population with similar socioeconomic status from area with no arsenic contamination **Population-Level Exposure:** not available	**Outcome: IFN-gamma concentration (pg/mL)** ***exposure status, unitless*** Exp. Level / n / mean / (CI) unexposed / NR / 1,372.3 / n/a individuals with arsenicosis / NR / 7.9 / n/a Stat Method: Mann-Whitney U test **Outcome: IL-10 concentration (pg/mL)** ***exposure status, unitless*** Exp. Level / n / mean / (CI) unexposed / NR / 90.3 / n/a individuals / NR / 4.6 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
arsenic induced skin lesions n cases: 20 n control: 18		with arsenicosis Stat Method: Mann-Whitney U test **Outcome: IL-2 concentration (pg/mL)** ***exposure status, unitless*** Exp. Level / n / mean / (CI) unexposed individuals / NR / 398.5 / n/a with arsenicosis / NR / 12.7 / n/a Stat Method: Mann-Whitney U test **Outcome: IL-4 concentration (pg/mL)** ***exposure status, unitless*** Exp. Level / n / mean / (CI) unexposed individuals / NR / 142.2 / n/a with arsenicosis / NR / 4.7 / n/a Stat Method: Mann-Whitney U test **Outcome: IL-5 concentration (pg/mL)** ***exposure status, unitless*** Exp. Level / n / mean / (CI) unexposed individuals / NR / 143.9 / n/a with arsenicosis / NR / 1.4 / n/a Stat Method: Mann-Whitney U test **Outcome: TNF-alpha concentration (pg/mL)** ***exposure status, unitless*** Exp. Level / n / mean / (CI) unexposed individuals / NR / 1,852.5 / n/a with arsenicosis / NR / 6.7 / n/a Stat Method: Mann-Whitney U test **Outcome: [3H] TdR incorporation (cpm)** ***exposure status + ConA dose (µg/mL), unitless*** Exp. Level / n / mean / (CI) unexposed + 0 µg/mL / NR / 1713.95 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		ConA individuals with arsenicosis + 0 µg/mL ConA NR 2929.34 n/a unexposed + 3 µg/mL ConA NR 5642.51 n/a individuals with arsenicosis + 3 µg/mL ConA NR 1862.538 n/a unexposed + 5 µg/mL ConA NR 8199.8 n/a individuals with arsenicosis + 5 µg/mL ConA NR 1365.75 n/a Stat Method: Mann-Whitney U test
Bosnjak et al. (2008) **Study Type:** cross-sectional **Location:** Croatia (Andrijasevci) **Population:** adult residents of village with history of higher than average arsenic in drinking water n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from single sample for each individual **Population-Level Exposure:** 627.72 µg/g-creatinine mean, 199.5-1,206.29 µg/g-creatinine range	**Outcome: B12** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / corr coeff / (CI) continuous NR 0.48 n/a Stat Method: Spearman rank correlation
García-Esquinas et al. (2013) **Study Type:** cohort	**Exposure Surrogate:** urine **Exposure Description:** individual urine samples collected and analyzed for	**Outcome: lymphatic and hematopoietic cancer** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th percentiles 40 0.46 0.22, 0.96

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	arsenic speciation **Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	Stat Method: Cox proportional hazard models; log transformed
Josyula et al. (2006) **Study Type:** cross-sectional **Location:** United States (Tucson and Ajo, Arizona) **Population:** adult residents using household tap water in Ajo (mean As water concentration 20.3+-3.7 µg/L) and Tucson (mean As water concentration 4.0 +- 2.3 µg/L) n cases: 40 n control: 33	**Exposure Surrogate:** urine **Exposure Description:** first morning void urine sample collected, analyzed for inorganic arsenic and metabolites and adjusted for creatinine; urine samples with creatinine <30 mg/dL or >300 mg/dL excluded from analysis; arsenic in toenail samples also analyzed **Population-Level Exposure:** 22 µg/L mean	**Outcome: ln (MMP-2/TIMP-1)** ***urinary inorganic arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR 0.028 n/a Stat Method: multiple linear regression **Outcome: ln (MMP-9/TIMP-1)** ***urinary inorganic arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR 0.031 n/a Stat Method: multiple linear regression **Outcome: ln MMP-2** ***urinary inorganic arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.018 n/a Stat Method: multiple linear regression **Outcome: ln MMP-9** ***urinary inorganic arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.017 n/a Stat Method: multiple linear regression **Outcome: ln TIMP-1** ***urinary inorganic arsenic concentration, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.049 n/a Stat Method: multiple linear regression
Lewis et al. (1999) **Study Type:** cohort	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic	**Outcome: lymphatic, hematopoietic tissue cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level n SMR (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(retrospective) **Location:** United States (Millard County, Utah) **Population:** male and female members of Latter-day Saints church wards n exposed: 2,203 n total: 2,203	concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	<1,000 NR 0.94 n/a 1,000-4,999 NR 0.68 n/a ≥ 5,000 NR 0.45 n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 NR 0.95 n/a 1,000-4,999 NR 0.65 n/a ≥ 5,000 NR 0.64 n/a Stat Method: standardized mortality ratios
Moore et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** infants born in rural Bangladesh; mothers are participants in MINIMat study n total: 1,556	**Exposure Surrogate:** maternal urine **Exposure Description:** sum of metabolites of inorganic arsenic measured in spot urine samples; adjusted for variation in urine dilution by specific gravity (mean 1.0012 g/mL) **Population-Level Exposure:** 102 µg/L median, 5.5-1,150 µg/L range	**Outcome: thymic index** ***maternal urinary arsenic concentration at week 52, µg/L*** Exp. Level / n / chi-square / (CI) continuous NR 12.93 n/a Stat Method: multiple linear regression with quadratic term for As **Outcome: thymic index/weight ratio** ***maternal urinary arsenic concentration at week 52, µg/L*** arsenic not significantly associated with thymic index/weight ratio
Pesola et al. (2012) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) participants n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** well water arsenic concentration **Population-Level Exposure:** 7-179 µg/L range	**Outcome: dyspnoea** ***well water arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <7 NR 1 n/a 7 -<39 NR 1.36 0.97, 1.9 39 -<91 NR 1.96 1.43, 2.7 91 -<179 NR 2.14 1.56, 2.92 ≥ 179 NR 1.8 1.31, 2.49 Stat Method: logistic regression; Chi-squared test for trend
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic concentration measured in single spot samples and adjusted by creatinine concentration and stratified by quintile	**Outcome: dyspnoea** ***urinary arsenic concentration (quintiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) quintile 1 NR 1 n/a quintile 2 NR 1.37 0.97, 1.92 quintile 3 NR 1.92 1.38, 2.65

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	Population-Level Exposure: not available	quintile 4 NR 1.94 1.41, 2.68 quintile 5 NR 1.87 1.36, 2.58 Stat Method: logistic regression; Chi-squared test for trend
Raqib et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** women and infants enrolled in MINIMat study of nutritional impact on fetal and infant development n total: 140	**Exposure Surrogate:** urine **Exposure Description:** maternal urine samples taken at gestation week 8 or 30 analyzed for inorganic arsenic and metabolites; samples adjusted for specific gravity **Population-Level Exposure:** 145.8 µg/L mean 186.8SD	**Outcome: breast milk concentration of IL-7 at 12 months** ***maternal urinary arsenic at gestation week 30, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.04 -0.07, -0.02 Stat Method: multivariate linear regression **Outcome: breast milk concentration of LtF at 12 months** ***maternal urinary arsenic at gestation week 30, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.002 -0.003, -0.001 Stat Method: multivariate linear regression **Outcome: thymic index at 2 months** ***maternal urinary arsenic at gestation week 30, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.01 -0.02, -0.001 Stat Method: multivariate linear regression **Outcome: thymus index at 12 months** ***maternal urinary arsenic at gestation week 30, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.012 -0.02, -0.002 Stat Method: multivariate linear regression **Outcome: thymus index at 6 months** ***maternal urinary arsenic at gestation week 30, µg/L*** Exp. Level n adjBeta (CI) continuous NR -0.015 -0.02, -0.005 Stat Method: multivariate linear regression
Shiue (2013)	**Exposure Surrogate:** urine	**Outcome: food sensitization - egg** ***urinary total arsenic, unitless*** total arsenic not significantly associated with food

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cross-sectional **Location:** United States (national) **Population:** NHANES n cases: 4,979 n control: n/a	**Exposure Description:** urine samples collected from individuals **Population-Level Exposure:** not available	sensitization **Outcome: food sensitization - milk** ***urinary total arsenic, unitless*** total arsenic not significantly associated with food sensitization **Outcome: food sensitization - peanut** ***urinary total arsenic, unitless*** total arsenic not significantly associated with food sensitization **Outcome: food sensitization - shrimp** ***urinary total arsenic, unitless*** total arsenic not significantly associated with food sensitization
Sohel et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** Health and Demographic Surveillance System 1991-2000, adults and children with nonaccidental deaths 1991-2000 n exposed: 93,415 n total: 93,415	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative drinking water arsenic concentration based on current arsenic concentrations (reasonably stable over time); average household exposure (used as proxy for individual exposure) calculated for each calendar year from 1970, based on information obtained from the current population present in that specific household for each year **Population-Level Exposure:** 10-300 µg/L range	**Outcome: all infections deaths** ***cumulative water arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <10 / 235 / 1 / n/a 10-49 / 286 / 1.09 / 0.92, 1.30 50-149 / 883 / 1.3 / 1.13, 1.49 150-299 / 783 / 1.51 / 1.31, 1.75 ≥ 300 / 295 / 1.59 / 1.33, 1.91 Stat Method: Cox proportional hazard model
Wu et al. (2012b) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** random selection of adults over	**Exposure Surrogate:** drinking water **Exposure Description:** water samples and geographic coordinates collected for 10,971 contiguous wells in a well-defined geographic area; participants used one of the tested wells **Population-Level Exposure:** 0.1-500.62 µg/L range	**Outcome: MMP-9 (ng/mL)** ***per Log-transformed well water arsenic, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 1 / 0.98, 1.02 Stat Method: computed with the log-transformed arsenic level entered as a continuous variable in linear regression models ***baseline concentrations of well water arsenic (quartiles), µg/L*** Exp. Level / n / adjBeta / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
age 30 enrolled in HEALS study n cases: 666 n control: n/a		0.10-2.0 NR 1 n/a 2.01-23.13 NR 0.88 0.77, 0.99 23.14-73.46 NR 0.96 0.85, 1.08 73.47 - 500.62 NR 0.99 0.88, 1.12 Stat Method: models run with log transformed inflammatory markers **Outcome: Myeloperoxidase (ng/mL)** ***per Log-transformed well water arsenic, µg/L*** Exp. Level n adjBeta (CI) continuous NR 1 0.97, 1.02 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models ***baseline concentrations of well water arsenic (quartiles), µg/L*** Exp. Level n adjBeta (CI) 0.10-2.0 NR 1 n/a 2.01-23.13 NR 0.94 0.83, 1.07 23.14-73.46 NR 0.96 0.84, 1.09 73.47 - 500.62 NR 0.99 0.87, 1.13 Stat Method: models run with log transformed inflammatory markers **Outcome: PAI-1 (ng/mL)** ***per Log-transformed well water arsenic, µg/L*** Exp. Level n adjBeta (CI) continuous NR 1.02 0.99, 1.04 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models ***baseline concentrations of well water arsenic (quartiles), µg/L*** Exp. Level n adjBeta (CI) 0.10-2.0 NR 1 n/a 2.01-23.13 NR 0.98 0.87, 1.10 23.14-73.46 NR 0.95 0.84, 1.07 73.47 - 500.62 NR 1.13 1.00, 1.28 Stat Method: models run with log transformed inflammatory markers

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: Soluble E-selectin (ng/mL) ***per Log-transformed well water arsenic, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 1 / 0.98, 1.02 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models ***baseline concentrations of well water arsenic (quartiles), µg/L*** Exp. Level / n / adjBeta / (CI) 0.10-2.0 / NR / 1 / n/a 2.01-23.13 / NR / 1 / 0.91, 1.09 23.14-73.46 / NR / 0.99 / 0.90, 1.08 73.47 - 500.62 / NR / 1 / 0.91, 1.10 Stat Method: models run with log transformed inflammatory markers **Outcome: Soluble ICAM-1 (ng/mL)** ***per Log-transformed well water arsenic, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 1 / 0.97, 1.03 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models ***baseline concentrations of well water arsenic (quartiles), µg/L*** Exp. Level / n / adjBeta / (CI) 0.10-2.0 / NR / 1 / n/a 2.01-23.13 / NR / 0.87 / 0.75, 1.00 23.14-73.46 / NR / 0.9 / 0.78, 1.04 73.47 - 500.62 / NR / 0.99 / 0.86, 1.15 Stat Method: models run with log transformed inflammatory markers **Outcome: Soluble VCAM-1 (ng/mL)** ***per Log-transformed well water arsenic, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 1.02 / 1.01, 1.03 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		baseline concentrations of well water arsenic (quartiles), µg/L Exp. Level / n / adjBeta / (CI) 0.10-2.0 / NR / 1 / n/a 2.01-23.13 / NR / 1.04 / 0.97, 1.12 23.14-73.46 / NR / 1.09 / 1.02, 1.17 73.47 - 500.62 / NR / 1.09 / 1.01, 1.16 Stat Method: models run with log transformed inflammatory markers
	Exposure Surrogate: urine **Exposure Description:** total urinary arsenic concentration measured by atomic absorption; all the urine samples were detectable for total urinary arsenic. **Population-Level Exposure:** 12.05-1,869.57 µg/g-creatinine range	**Outcome: MMP-9 (ng/mL)**
		per Log-transformed urinary arsenic, µg/g-creatinine Exp. Level / n / adjBeta / (CI) continuous / NR / 0.98 / 0.93, 1.03 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models
		baseline concentrations of urinary arsenic (quartiles), µg/g-creatinine Exp. Level / n / adjBeta / (CI) 12.05-88.21 / NR / 1 / n/a 88.22-141.69 / NR / 0.89 / 0.79, 1.01 141.70-275.63 / NR / 0.86 / 0.76, 0.97 275.64-1,869.57 / NR / 0.95 / 0.84, 1.08 Stat Method: models run with log transformed inflammatory markers
		Outcome: Myeloperoxidase (ng/mL)
		per Log-transformed urinary arsenic, µg/g-creatinine Exp. Level / n / adjBeta / (CI) continuous / NR / 0.98 / 0.93, 1.03 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models
		baseline concentrations of urinary arsenic (quartiles), µg/g-creatinine Exp. Level / n / adjBeta / (CI) 12.05-88.21 / NR / 1 / n/a 88.22-141.69 / NR / 0.87 / 0.76, 0.99

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		141.70-275.63 NR 0.91 0.80, 1.03 275.64-1,869.57 NR 0.92 0.81, 1.05 Stat Method: models run with log transformed inflammatory markers
		Outcome: PAI-1 (ng/mL)
		per Log-transformed urinary arsenic, µg/g-creatinine Exp. Level n adjBeta (CI) continuous NR 1.05 1.00, 1.11 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models
		baseline concentrations of urinary arsenic (quartiles), µg/g-creatinine Exp. Level n adjBeta (CI) 12.05-88.21 NR 1 n/a 88.22-141.69 NR 0.96 0.85, 1.09 141.70-275.63 NR 0.95 0.84, 1.07 275.64-1,869.57 NR 1.11 0.90, 1.26 Stat Method: models run with log transformed inflammatory markers
		Outcome: Soluble E-selectin (ng/mL)
		per Log-transformed urinary arsenic, µg/g-creatinine Exp. Level n adjBeta (CI) continuous NR 1 0.96, 1.04 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models
		baseline concentrations of urinary arsenic (quartiles), µg/g-creatinine Exp. Level n adjBeta (CI) 12.05-88.21 NR 1 n/a 88.22-141.69 NR 0.96 0.88, 1.06 141.70-275.63 NR 0.92 0.84, 1.01 275.64-1,869.57 NR 0.99 0.90, 1.09

Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: models run with log transformed inflammatory markers
		Outcome: Soluble ICAM-1 (ng/mL)
		per Log-transformed urinary arsenic, µg/g-creatinine Exp. Level / n / adjBeta / (CI) continuous / NR / 1.01 / 0.95, 1.07 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models
		baseline concentrations of urinary arsenic (quartiles), µg/g-creatinine Exp. Level / n / adjBeta / (CI) 12.05-88.21 / NR / 1 / n/a 88.22-141.69 / NR / 0.92 / 0.79, 1.06 141.70-275.63 / NR / 0.96 / 0.83, 1.11 275.64-1,869.57 / NR / 1 / 0.86, 1.16 Stat Method: models run with log transformed inflammatory markers
		Outcome: Soluble VCAM-1 (ng/mL)
		per Log-transformed urinary arsenic, µg/g-creatinine Exp. Level / n / adjBeta / (CI) continuous / NR / 1.04 / 1.01, 1.07 Stat Method: computed with log-transformed arsenic level entered as a continuous variable in linear regression models
		baseline concentrations of urinary arsenic (quartiles), µg/g-creatinine Exp. Level / n / adjBeta / (CI) 12.05-88.21 / NR / 1 / n/a 88.22-141.69 / NR / 1.02 / 0.95, 1.09 141.70-275.63 / NR / 1.08 / 1.01, 1.16 275.64-1,869 / NR / 1.09 / 1.02, 1.17 Stat Method: models run with log transformed inflammatory markers

--: not reported; n: number of cases (when presented in Results column)

5.8.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Immune System and Lymphatic Effects

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5.9 Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults) n exposed: 56,378 n total: 57,053	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** not available	**Outcome: liver cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 0.99 / 0.89, 1.10 Stat Method: Cox regression
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** 0.7 µg/L median	**Outcome: liver cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 1.05 / 0.88, 1.25 Stat Method: Cox regression
Chung et al. (2012) **Study Type:** cohort (prospective) **Location:** Taiwan (Homei, Fuhsin, Hsinming)	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure assessment determined by duration of artesian well water use, history or residence, and historical data; cumulative arsenic exposure derived to reflect long-term arsenic exposure by median well water arsenic (population	**Outcome: liver cancer** ***cumulative water arsenic exposure (tertiles), µg/L-year*** Exp. Level / n / adjOR / (CI) <9.1 / 5 / 1 / n/a 9.1-19.5 / 11 / 1.46 / 0.49, 4.37 ≥ 19.5 / 8 / 0.65 / 0.17, 2.44 Stat Method: Cox proportional hazard model

Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Population: residents of arseniasis-endemic areas n total: 1,563	level exposure reported here) x duration of use **Population-Level Exposure:** 9.1-19.5 µg/L-year range	
	Exposure Surrogate: drinking water **Exposure Description:** information on median arsenic level in artesian well water of each village acquired from previous studies carried out in the early 1960s (Lai et al., 1994); some study subjects had moved from one village to another, and there were differences in arsenic concentrations between villages **Population-Level Exposure:** 0.7-0.93 mg/L range	**Outcome: liver cancer** ***average water arsenic concentration (tertiles), mg/L*** Exp. Level / n / HR / (CI) <0.05 / 3 / 1 / n/a 0.05-0.71 / 12 / 1.29 / 0.34, 4.83 ≥ 0.71 / 9 / 0.87 / 0.22, 3.50 Stat Method: Cox proportional hazard model
	Exposure Surrogate: urine **Exposure Description:** urine samples of 1,078 subjects collected at time of recruitment; all arsenic assays performed within 6 months of sample collection **Population-Level Exposure:** not available	**Outcome: liver cancer** ***percent DMA in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) ≥ 85.8 / 3 / 1 / n/a 76.13-85.8 / 7 / 1.67 / 0.43, 6.52 <76.13 / 6 / 1.01 / 0.25, 4.13 Stat Method: Cox proportional hazard model ***percent inorganic arsenic in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) <4.22 / 3 / 1 / n/a 4.22-7.86 / 4 / 1.05 / 0.23, 4.70 ≥ 7.86 / 9 / 2.32 / 0.63, 8.64 Stat Method: Cox proportional hazard model ***percent MMA in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) <8.34 / 3 / 1 / n/a 8.34-15.31 / 8 / 2.57 / 0.68, 9.72 ≥ 15.31 / 5 / 0.8 / 0.19, 3.38 Stat Method: Cox proportional hazard model
García-Esquinas et al.	**Exposure Surrogate:** urine	**Outcome: liver, gallbladder, and bile duct cancer**

Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(2013) **Study Type:** cohort (prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	**Exposure Description:** individual urine samples collected and analyzed for arsenic speciation **Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th percentiles / NR / 1.34 / 0.66, 2.72 Stat Method: Cox proportional hazard models; log transformed
Guo et al. (2007) **Study Type:** cross-sectional **Location:** Mongolia region not available **Population:** residents of villages in the Hetao Plain, Inner Mongolia n cases: 680 n control: 189	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic samples were taken from 94 water sources, including wells; detection limit not specified, but authors note reliability of the method at <10 µg/L; arsenic exposure determined by location of village **Population-Level Exposure:** 50-1,860 µg/L range	**Outcome: hepatomegaly** ***water arsenic concentration, µg/L*** arsenic not significantly associated with hepatomegaly **Outcome: liver function test** ***water arsenic concentration, µg/L*** arsenic not significantly associated with liver function
Hsu et al. (2013b) **Study Type:** cohort (prospective) **Location:** Taiwan (SW: Peimen, Hsuechia, Ichu, and Putai Townships; NE: Chiaohsi, Chuangwei, Wuchieh, and Tungshan Townships) **Population:** residents of an arseniasis-endemic area with and	**Exposure Surrogate:** drinking water **Exposure Description:** SW population: median arsenic level of several wells shared in a village derived from two surveys; NE population: arsenic level of well water samples collected during home interviews **Population-Level Exposure:** 10-500 µg/L range	**Outcome: liver cancer** ***arsenic concentration in well water (non-diabetes mellitus vs. diabetes mellitus subjects), µg/L*** Exp. Level / n / HR / (CI) non-DM w/ As <500 / NR / 1 / n/a DM w/ As <500 / NR / 2.63 / 1.84, 3.76 non-DM w/ As ≥ 500 / NR / 1 / n/a DM w/ As ≥ 500 / NR / 2.32 / 1.11, 4.86 Stat Method: Cox regression analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects		
Reference and Study Design	**Exposure Measures**	**Results**
without skin lesions n total: 9,525		
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2,203 n total: 2,203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: billiary passages and liver cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / 2.99 / n/a 1,000-4,999 / NR / NR / n/a ≥ 5,000 / NR / 1.15 / n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1,000 / NR / NR / n/a 1,000-4,999 / NR / 2.52 / n/a ≥ 5,000 / NR / NR / n/a Stat Method: standardized mortality ratios
Majumdar et al. (2009) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** residents of arsenic-affected villages with comparison population from low exposure area n cases: 3,825 n control: 3,451	**Exposure Surrogate:** drinking water **Exposure Description:** for each participant, water samples from private or public tube wells analyzed for arsenic; exposure categories developed based on arsenic levels **Population-Level Exposure:** 50-500 µg/L range	**Outcome: hepatomegaly** ***arsenic concentration in drinking water (females), µg/L*** Exp. Level / n / prevOR / (CI) <50 / NR / 1 / n/a ≥ 500 / NR / 4.34 / 2.8, 6.5 Stat Method: prevalence odds ratio calculated for each outcome comparing highest and lowest exposure levels ***arsenic concentration in drinking water (males), µg/L*** Exp. Level / n / prevOR / (CI) <50 / NR / 1 / n/a ≥ 500 / NR / 5.13 / 3.4, 7.6 Stat Method: prevalence odds ratio calculated for each outcome comparing highest and lowest exposure levels
Sawada et al. (2013) **Study Type:** cohort (prospective) **Location:** Japan (Iwate, Akita, Nagano,	**Exposure Surrogate:** diet **Exposure Description:** detailed questionnaire on food intake/frequency; average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each	**Outcome: liver cancer** ***inorganic arsenic intake (females; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.6 / 21 / 1 / n/a 53.7 / 32 / 1.36 / 0.78, 2.38 62.6 / 36 / 1.41 / 0.81, 2.46 105.7 / 28 / 1.1 / 0.61, 1.97

Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90,378	item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	Stat Method: Multivariate regression ***inorganic arsenic intake (males; quartiles), µg/day*** Exp. Level / n / HR / (CI) 40.5 / 68 / 1 / n/a 54.7 / 49 / 0.62 / 0.43, 0.90 63.5 / 78 / 0.87 / 0.62, 1.22 99.1 / 90 / 0.94 / 0.67, 1.31 Stat Method: Multivariate regression
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho) **Population:** adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	**Outcome: liver cancer** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 / 0 / 0 / 0, 4.43 0.05-0.99 / 0 / 0 / 0, 15.06 ≥ 1 / 2 / 7.17 / 1.28, 26.05 Stat Method: Cox proportional hazard

--: not reported; n: number of cases (when presented in Results column)

5.9.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects

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5.10 Summary of Observational Epidemiology Studies for Health Effect Category: Mortality

Summary of Observational Epidemiology Studies for Health Effect Category: Mortality		
Reference and Study Design	**Exposure Measures**	**Results**
Rahman et al. (2013) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** children in AsMat study who died non-accidental deaths n total: 185	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure based on number of years each well used and concentration in each well **Population-Level Exposure:** 1,000-4,000 ug-yr/L range	**Outcome: all-cause mortality** ***cumulative water arsenic exposure, ug-yr/L*** Exp. Level / n / HR / (CI) <1,000 / 54 / 1 / n/a 1,000-4,000 / 88 / 1.17 / 0.84, 1.65 >4,000 / 43 / 1.9 / 1.25, 2.89 Stat Method: Cox proportional hazard
	Exposure Surrogate: drinking water **Exposure Description:** well water samples (n = 13,286) analyzed for determination of baseline individual-level arsenic exposure; historical drinking water exposure information obtained from parent/guardian interviews; baseline, time- weighted lifetime average, and cumulative arsenic exposure estimated for each individual **Population-Level Exposure:** 10-300 µg/L range	**Outcome: all-cause mortality** ***baseline water arsenic concentration (quintiles), µg/L*** Exp. Level / n / HR / (CI) <10 / 83 / 1 / n/a 10-49 / 15 / 1.13 / 0.65, 1.96 50-149 / 13 / 0.81 / 0.45, 1.46 150-299 / 39 / 1.35 / 0.92, 1.97 300+ / 35 / 1.51 / 1.01, 2.23 Stat Method: Cox proportional hazard
		time-weighted lifetime average arsenic concentration (quintiles), µg/L Exp. Level / n / HR / (CI) <10 / 24 / 1 / n/a 10-49 / 17 / 1.37 / 0.74, 2.57 50-149 / 44 / 1.44 / 0.88, 2.38 150-299 / 56 / 1.22 / 0.75, 1.98 300+ / 44 / 1.88 / 1.14, 3.10 Stat Method: Cox proportional hazard
		Outcome: cancer and cardiovascular-related mortality ***baseline water arsenic concentration quartiles), µg/L*** Exp. Level / n / HR / (CI) <10 / 16 / 1 / n/a 10-50 / 4 / 1.53 / 0.51, 4.57 51-150 / 4 / 1.29 / 0.43, 3.87

Summary of Observational Epidemiology Studies for Health Effect Category: Mortality		
Reference and Study Design	**Exposure Measures**	**Results**
		>150 22 2.18 1.15, 4.16 Stat Method: Cox proportional hazard
Sohel et al. (2009) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** Health and Demographic Surveillance System 1991-2000, adults and children with nonaccidental deaths 1991-2000 n exposed: 93,415 n total: 93,415	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative drinking water arsenic concentration based on current arsenic concentrations (reasonably stable over time); average household exposure (used as proxy for individual exposure) calculated for each calendar year from 1970, based on information obtained from the current population present in that specific household for each year **Population-Level Exposure:** 10-300 µg/L range	**Outcome: all nonaccidental deaths** ***cumulative water arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <10 967 1 n/a 10-49 1,258 1.16 1.06, 1.26 50-149 3,584 1.26 1.18, 1.36 150-299 3,077 1.36 1.27, 1.47 ≥ 300 1,076 1.35 1.23, 1.48 Stat Method: Cox proportional hazard model **Outcome: cancer deaths** ***cumulative water arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <10 55 1 n/a 10-49 71 1.1 0.77, 1.59 50-149 229 1.44 1.06, 1.95 150-299 181 1.75 1.28, 2.40 ≥ 300 53 1.06 1.56, 2.30 Stat Method: Cox proportional hazard model
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho) **Population:** adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	**Outcome: all deaths** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 56 0.87 0.67, 1.13 0.05-0.99 17 1.08 0.65, 1.73 ≥ 1 32 1.58 1.12, 2.22 Stat Method: Cox proportional hazard

--: not reported; n: number of cases (when presented in Results column)

5.10.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Mortality

Rahman, M; Sohel, N; Yunus, M; Chowdhury, ME; Hore, SK; Zaman, K; Bhuiya, A; Streatfield, PK. (2013). Increased childhood mortality and arsenic in drinking water in Matlab, Bangladesh: a population-based cohort study. PLoS ONE 8: e55014. http://dx.doi.org/10.1371/journal.pone.0055014

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Tsuda, T; Babazono, A; Yamamoto, E; Kurumatani, N; Mino, Y; Ogawa, T; Kishi, Y; Aoyama, H. (1995). Ingested arsenic and internal cancer: A historical cohort study followed for 33 years. Am J Epidemiol 141: 198-209.

5.11Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Adams et al. (2013) **Study Type:** case-control **Location:** United States (AZ) **Population:** children with autism; participants recruited with help of the Autism Society of America—Greater Phoenix Chapter and the Arizona Division of Developmental Disabilities n cases: 55 n control: 44	**Exposure Surrogate:** blood **Exposure Description:** morning blood samples collected after overnight fast; RBC samples provided a measure of longer-term exposure (several months) **Population-Level Exposure:** 4.32 ng/g mean	**Outcome: autism** ***arsenic concentration in RBC, ng/g*** Exp. Level / n / mean / (CI) neurotypical group: NR / 4.33 / n/a autism group: NR / 4.3 / n/a Stat Method: two-sided unpaired t-test
	Exposure Surrogate: blood **Exposure Description:** morning blood samples collected after overnight fast; whole blood samples included a mixture of long-term (cellular) and short-term (serum) components and provided a measure of intermediate exposure **Population-Level Exposure:** 3.33 µg/L mean	**Outcome: autism** ***whole blood arsenic concentrations, µg/L*** Exp. Level / n / mean / (CI) neurotypical group: NR / 3.37 / n/a autism group: NR / 3.3 / n/a Stat Method: two-sided unpaired t-test
	Exposure Surrogate: blood and urine **Exposure Description:** blood and urine exposure (combined) as continuous variable **Population-Level Exposure:** not available	**Outcome: autism (severity/symptoms determined by pervasive developmental disorder behavior inventory [PDD-BI])** ***toxic metals in blood and urine, unitless*** Exp. Level / n / adjR2 / (CI) continuous: NR / 0.46 / n/a Stat Method: regression
	Exposure Surrogate: urine **Exposure Description:** morning urine samples collected after overnight fast (first urine); provided a measure of recent exposure (several days)	**Outcome: autism** ***arsenic concentration in urine by autism status, µg/g-creatinine*** Exp. Level / n / mean / (CI) neurotypical group: NR / 17.9 / n/a autism group: NR / 30.8 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	Population-Level Exposure: 24.35 µg/g-creatinine mean	Stat Method: two-sided unpaired t-test
Ali et al. (2010) **Study Type:** cross-sectional **Location:** Bangladesh (Kushtia district (northwest)) **Population:** residents of areas with high prevalence of arsenicosis n cases: 141 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** water samples collected from tube wells and analyzed for total arsenic; all samples determined in triplicate and average values used for data analysis; study subjects split into tertile groups based on drinking water arsenic concentrations **Population-Level Exposure:** 224.92 µg/L mean 57.2SD	**Outcome: plasma cholinesterase (PChE) activity (U/L) x 10^4** ***water arsenic levels (by regulatory limits), µg/L*** Exp. Level / n / mean / (CI) ≤ 50 / NR / 1.775 / n/a >50 / NR / 1.365 / n/a Stat Method: Independent Samples T-Test ***Log water arsenic concentration, µg/L*** Exp. Level / n / corr coeff / (CI) continuous / NR / -0.52 / n/a Stat Method: Spearman correlation coefficient test
	Exposure Surrogate: hair **Exposure Description:** hair samples ~1 cm long were collected from close to the scalp, behind the ear; cleaned prior to analysis **Population-Level Exposure:** 5.27 µg/g mean 7.06SD	**Outcome: plasma cholinesterase (PChE) activity (U/L) x 10^4** ***log hair arsenic levels, µg/g*** Exp. Level / n / corr coeff / (CI) continuous / NR / -0.47 / n/a Stat Method: Spearman correlation coefficient test
	Exposure Surrogate: nail **Exposure Description:** individual nail samples collected and cleaned prior to analysis **Population-Level Exposure:** 7.51 µg/g mean 7.64SD	**Outcome: plasma cholinesterase (PChE) activity (U/L) x 10^4** ***log nail arsenic levels, µg/g*** Exp. Level / n / corr coeff / (CI) continuous / NR / -0.35 / n/a Stat Method: Spearman correlation coefficient test
Chiou et al. (2005) **Study Type:** cohort (retrospective) **Location:** Taiwan (southwestern: Tainan	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration as reported by the National Taiwan University Group; median concentration used as surrogate if village had multiple wells	**Outcome: Neurological disorder** ***drinking water arsenic concentration - non-diabetic subjects, mg/L*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-0.29 / NR / 0.84 / 0.73, 0.97 0.3-0.59 / NR / 1.1 / 0.98, 1.25 ≥ 0.6 / NR / 1.68 / 1.49, 1.89

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
County (Yenshui, Beimen, and Shuechia townships), Chiayi County (Putai and Yichu townships)) **Population:** adults and children living in arseniasis-endemic townships n total: 28,499	**Population-Level Exposure:** 0.1-0.6 mg/L range	Stat Method: Stratified analysis and unconditional logistic regression ***drinking water arsenic concentration - Type 2 diabetic subjects, mg/L*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-0.29 / NR / 1.08 / 0.73, 1.60 0.3-0.59 / NR / 1.8 / 1.32, 2.46 ≥ 0.6 / NR / 2.78 / 2.01, 3.85 Stat Method: Stratified analysis and unconditional logistic regression
Ghosh et al. (2007b) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** West Bengal residents exposed to arsenic in drinking water with and without skin lesions and similar unexposed residents n cases: 725 n control: 389	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic content in drinking water measured from 100 ml samples provided by study participants; instrument calibrated and readings taken in duplicate for each sample **Population-Level Exposure:** 0-1,188 µg/L range	**Outcome: conjunctivitis** ***arsenic exposure/skin lesion status, unitless*** Exp. Level / n / adjOR / (CI) unexposed / 13 / 1 / n/a exposed, no skin lesions / 44 / 4.66 / 2.45, 8.85 exposed, skin lesions / 208 / 37.22 / 20.56, 67.36 Stat Method: Logistic regression analysis **Outcome: peripheral neuropathy** ***arsenic exposure/skin lesion status, unitless*** Exp. Level / n / adjOR / (CI) unexposed / 11 / 1 / n/a exposed, no skin lesions / 33 / 3.99 / 1.95, 8.09 exposed, skin lesions / 114 / 15.61 / 8.2, 29.71 Stat Method: Logistic regression analysis
Guo et al. (2007) **Study Type:** cross-sectional **Location:** Mongolia (region not available) **Population:** residents of villages in the Hetao Plain, Inner Mongolia	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic samples were taken from 94 water sources, including wells; detection limit not specified, but authors note reliability of the method at <10 µg/L; arsenic exposure determined by location of village **Population-Level Exposure:**	**Outcome: blurred vision** ***water arsenic concentration, µg/L*** Exp. Level / n / Prev / (CI) ≤ 50 µg/L / NR / 3.7 / n/a >50 µg/L / NR / 17.35 / n/a Stat Method: not reported **Outcome: loss of hearing** ***water arsenic concentration, µg/L*** Exp. Level / n / Prev / (CI) ≤ 50 µg/L / NR / 1.06 / n/a >50 µg/L / NR / 5.88 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
n cases: 680 n control: 189	50-1,860 µg/L range (≤ 50 µg/L unaffected villages; >50 µg/L affected villages)	Stat Method: not reported **Outcome: loss of taste** ***water arsenic concentration, µg/L*** Exp. Level / n / Prev / (CI) ≤ 50 µg/L / NR / 0 / n/a >50 µg/L: / NR / 5.44 / n/a Stat Method: not reported **Outcome: numbness of limbs** ***water arsenic concentration, µg/L*** Exp. Level / n / Prev / (CI) ≤ 50 µg/L / NR / 0 / n/a >50 µg/L / NR / 33.53 / n/a Stat Method: not reported
Hafeman et al. (2005) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** subset of HEALS participants randomly selected at clinic for peripheral neuropathy assessment n cases: 137 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic index calculated by multiplying water arsenic concentration by estimated volume consumed yearly times years of water use **Population-Level Exposure:** 2.9-11,482 ug range	**Outcome: index finger vibration threshold** ***cumulative arsenic index (tertiles), ug*** Exp. Level / n / adjBeta / (CI) 2.9-159.1 / NR / NR / n/a 159.5-843.7 / NR / -0.087 / n/a 953.3-11,482.5 / NR / 0.038 / n/a Stat Method: Linear regression analyses ***cumulative arsenic index per 50 units, ug*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.00003 71 / n/a Stat Method: Linear regression analyses **Outcome: toe vibration threshold** ***cumulative arsenic index (tertiles), ug*** Exp. Level / n / adjBeta / (CI) 2.9-159.1 / NR / NR / n/a 159.5-843.7 / NR / -0.009 / n/a 953.3-11,482.5 / NR / 0.129 / n/a Stat Method: Linear regression analyses ***cumulative arsenic index per 50 units, ug*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.00251 / n/a Stat Method: Linear regression analyses
	Exposure Surrogate: drinking water	**Outcome: index finger vibration threshold**

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Description: drinking water samples obtained from wells of use at recruitment to HEALS **Population-Level Exposure:** 115 µg/L mean, 140SD, 5-743 µg/L range	***drinking water arsenic concentration (tertiles), µg/L*** Exp. Level / n / adjBeta / (CI) 5-23 / NR / NR / n/a 25-125 / NR / 0.058 / n/a 129-743 / NR / -0.013 / n/a Stat Method: Linear regression analyses
		drinking water arsenic concentration per 50 units, µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.013 / n/a Stat Method: Linear regression analyses
		Outcome: toe vibration threshold
		drinking water arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) 5-23 / NR / NR / n/a 25-125 / NR / -0.000585 / n/a 129-743 / NR / 0.203 / n/a Stat Method: Linear regression analyses
		drinking water arsenic concentration per 50 units, µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.025 / n/a Stat Method: Linear regression analyses
	Exposure Surrogate: urine **Exposure Description:** urine samples collected at recruitment into HEALS (2001) and again at recruitment into subcohort (2003); mean (SD) urinary As: 326.3 (307.5) in 2001 and 252.4 (185.4) in 2003 **Population-Level Exposure:** 25.5-1,736.9 µg/mg creatinine range	**Outcome: index finger vibration threshold**
		urinary arsenic concentration (2001) (tertiles), µg/mg creatinine Exp. Level / n / adjBeta / (CI) 25.5-148.7 / NR / NR / n/a 149.1-325.5 / NR / -0.106 / n/a 332.6-1,736.9 / NR / -0.068 / n/a Stat Method: Linear regression analyses
		urinary arsenic concentration (2003) (tertiles), µg/mg creatinine Exp. Level / n / adjBeta / (CI) 36.5-147 / NR / NR / n/a 150.8-270.5 / NR / -0.039 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		271.4-975.4 NR 0.129 n/a Stat Method: Linear regression analyses
		urinary arsenic concentration per 50 units (2001), µg/mg creatinine Exp. Level n adjBeta (CI) continuous NR -0.00364 n/a Stat Method: Linear regression analyses
		urinary arsenic concentration per 50 units (2003), µg/mg creatinine Exp. Level n adjBeta (CI) continuous NR -0.008 n/a Stat Method: Linear regression analyses
		Outcome: toe vibration threshold
		urinary arsenic concentration (2001) (tertiles), µg/mg creatinine Exp. Level n adjBeta (CI) 25.5-148.7 NR NR n/a 149.1-325.5 NR 0.019 n/a 332.6-1,736.9 NR 0.197 n/a Stat Method: Linear regression analyses
		urinary arsenic concentration (2003) (tertiles), µg/mg creatinine Exp. Level n adjBeta (CI) 36.5-147 NR NR n/a 150.8-270.5 NR -0.039 n/a 271.4-975.4 NR -0.138 n/a Stat Method: Linear regression analyses
		urinary arsenic concentration per 50 units (2001), µg/mg creatinine Exp. Level n adjBeta (CI) continuous NR 0.019 n/a Stat Method: Linear regression analyses
		urinary arsenic concentration per 50 units (2003), µg/mg creatinine Exp. Level n adjBeta (CI) continuous NR 0.014 n/a Stat Method: Linear regression analyses
Kreiss et al. (1983)	**Exposure Surrogate:** drinking water	**Outcome: abnormal [neuropathy] exam or**

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cross-sectional **Location:** United States (Ester Dome, Alaska) **Population:** adult residents under age 60 living for at least 2 years in area with known elevated levels of arsenic in well water n cases: 147 n control: 95	**Exposure Description:** daily arsenic ingestion calculated individually based on consumption information for both well water and water from other sources; arsenic concentrations of home well water analyzed **Population-Level Exposure:** 1-4521 µg/day range	**velocity** ***daily arsenic ingestion from drinking water, µg/day*** Exp. Level / n / Prev / (CI) 0-100 NR 17 n/a 101-1000 NR 12 n/a 1001-15000 NR 3 n/a Stat Method: multiple linear regression **Outcome: any conduction velocity below 5th percentile** ***daily arsenic ingestion from drinking water, µg/day*** Exp. Level / n / Prev / (CI) 0-100 NR 13 n/a 101-1000 NR 12 n/a 1001-15000 NR 2 n/a Stat Method: multiple linear regression **Outcome: neuropathy by examination** ***daily arsenic ingestion from drinking water, µg/day*** Exp. Level / n / Prev / (CI) 0-100 NR 4 n/a 101-1000 NR 1 n/a 1001-15000 NR 1 n/a Stat Method: multiple linear regression **Outcome: peroneal motor nerve velocity below 5th percentile** ***daily arsenic ingestion from drinking water, µg/day*** Exp. Level / n / Prev / (CI) 0-100 NR 4 n/a 101-1000 NR 6 n/a 1001-15000 NR 0 n/a Stat Method: multiple linear regression **Outcome: sural sensory nerve velocity below 5th percentile** ***daily arsenic ingestion from drinking water, µg/day*** Exp. Level / n / Prev / (CI) 0-100 NR 4 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		101-1000 NR 3 n/a 1001-15000 NR 1 n/a Stat Method: multiple linear regression
		Outcome: ulnar motor nerve velocity: elbow-axilla below 5th percentile
		daily arsenic ingestion from drinking water, µg/day Exp. Level / n / Prev / (CI) 0-100 NR 4 n/a 101-1000 NR 3 n/a 1001-15000 NR 0 n/a Stat Method: multiple linear regression
		Outcome: ulnar motor nerve velocity: wrist-elbow below 5th percentile
		daily arsenic ingestion from drinking water, µg/day Exp. Level / n / Prev / (CI) 0-100 NR 4 n/a 101-1000 NR 3 n/a 1001-15000 NR 1 n/a Stat Method: multiple linear regression
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2203 n total: 2203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: central nervous system cancer**
		cumulative arsenic exposure (females), ppb-years Exp. Level / n / SMR / (CI) <1000 NR 1.21 n/a 1000-4999 NR NR n/a ≥ 5000 NR NR n/a Stat Method: standardized mortality ratios
		cumulative arsenic exposure (males), ppb-years Exp. Level / n / SMR / (CI) <1000 NR NR n/a 1000-4999 NR 0.9 n/a ≥ 5000 NR NR n/a Stat Method: standardized mortality ratios
Li et al. (2006) **Study Type:** cross-sectional	**Exposure Surrogate:** drinking water **Exposure Description:** water samples obtained from wells of individual families	**Outcome: peripheral neuropathy - left arm**
		drinking water arsenic concentration, µg/L Exp. Level / n / regr coeff / (CI) <20 NR 1 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Location: China (Mongolia) **Population:** residents of Bamen region exposed to arsenic in drinking water n cases: 309 n control: n/a	or community water sources **Population-Level Exposure:** 0-700 µg/L range	100-300 NR 0.35 n/a 400-700 NR 1.7 n/a Stat Method: categorical multivariate analysis **Outcome: peripheral neuropathy - left leg** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / regr coeff / (CI) <20 NR 1 n/a 100-300 NR 1.41 n/a 400-700 NR 2.96 n/a Stat Method: categorical multivariate analysis **Outcome: peripheral neuropathy - right arm** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / regr coeff / (CI) <20 NR 1 n/a 100-300 NR 0.62 n/a 400-700 NR 1.51 n/a Stat Method: categorical multivariate analysis **Outcome: peripheral neuropathy - right leg** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / regr coeff / (CI) <20 NR 1 n/a 100-300 NR NR n/a 400-700 NR 2.16 n/a Stat Method: categorical multivariate analysis
Lin et al. (2008) **Study Type:** cross-sectional **Location:** Taiwan (Homei, Fuhsin, and Hsinming villages in Putai Township, Chiayi County) **Population:** residents of pterygium endemic	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated based on well water concentrations (1960 measurements), and duration of living in each village (obtained from questionnaire); exposure was classified as unknown if the arsenic concentration was unavailable for any village the participant had lived in **Population-Level Exposure:** 0.1-15.1 mg/L - yr range	**Outcome: pterygium** ***cumulative arsenic exposure concentration, mg/L - yr*** Exp. Level / n / adjOR / (CI) <0.1 NR 1 n/a 0.1-15.0 NR 2.04 1.04, 3.99 ≥ 15.1 NR 2.88 1.42, 5.83 unknown NR 1.1 0.45, 2.69 Stat Method: multiple logistic regression model

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
villages n cases: 223 n control: 160		
Otto et al. (2006) **Study Type:** cross-sectional **Location:** China (Bamen Region, Inner Mongolia, China) **Population:** children and adults in region with high arsenic concentrations who consumed water from wells n cases: 309 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** samples from individual and community wells analyzed; statistical analyses conducted to determine threshold in relationship between arsenic concentration and outcome **Population-Level Exposure:** 20-700 µg/L range	**Outcome: vibration threshold, dominant hand, digit 2** ***total water arsenic concentration, µg/L*** Exp. Level / n / corr coeff / (CI) <170 / NR / -0.25 / n/a >170 / NR / 0.2 / n/a Stat Method: log10 transformation and linear regression **Outcome: vibration threshold, dominant hand, digit 5** ***total water arsenic concentration, µg/L*** Exp. Level / n / corr coeff / (CI) <170 / NR / -0.55 / n/a >170 / NR / 0.4 / n/a Stat Method: log10 transformation and linear regression **Outcome: vibration threshold, non-dominant hand, digit 2** ***total water arsenic concentration, µg/L*** Exp. Level / n / corr coeff / (CI) <150 / NR / -0.31 / n/a >150 / NR / 0.36 / n/a Stat Method: log10 transformation and linear regression **Outcome: vibration threshold, non-dominant hand, digit 5** ***total water arsenic concentration, µg/L*** Exp. Level / n / corr coeff / (CI) <170 / NR / -0.51 / n/a >170 / NR / 0.4 / n/a Stat Method: log10 transformation and linear regression
Otto et al. (2007)	**Exposure Surrogate:** drinking water	**Outcome: pinprick score, left arm**

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cross-sectional **Location:** China (Farming region of Ba Men, Inner Mongolia) **Population:** residents from 9 to 64 years of age using wells in area with high arsenic concentrations in ground water n cases: 320 n control: n/a	**Exposure Description:** samples collected from 117 wells used by study participants on three consecutive days and results averaged across days); no speciation **Population-Level Exposure:** 270 µg/L mean 230SD	***drinking water arsenic concentration, µg/L*** Exp. Level n adjOR (CI) continuous NR 2.13 n/a Stat Method: multivariate regression; ordered logistic regression models
		drinking water arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 3.23 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, left leg
		drinking water arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 2.77 n/a Stat Method: multivariate regression; ordered logistic regression models
		drinking water arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 4.36 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, right arm
		drinking water arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 1.85 n/a Stat Method: multivariate regression; ordered logistic regression models
		drinking water arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 2.64 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, right leg
		drinking water arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 2.99 n/a Stat Method: multivariate regression;

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		ordered logistic regression models
		drinking water arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 4.65 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: vibration threshold, non-dominant hand, fifth digit
		drinking water arsenic concentration, µg/L Exp. Level n adjR2 (CI) continuous NR 0.11 n/a Stat Method: multivariate regression
		Outcome: vibration threshold, non-dominant hand, second digit
		drinking water arsenic concentration, µg/L Exp. Level n adjR2 (CI) continuous NR 0.11 n/a Stat Method: multivariate regression
	Exposure Surrogate: toenails **Exposure Description:** cleaned and washed toenail samples from each participant analyzed **Population-Level Exposure:** 11.85 µg/kg mean 11.85SD	**Outcome: pinprick score, left arm**
		toenail arsenic concentration, µg/kg Exp. Level n adjOR (CI) continuous NR 1.91 n/a Stat Method: multivariate regression; ordered logistic regression models
		toenail arsenic concentration, µg/kg Exp. Level n regr coeff (CI) continuous NR 0.0548 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, left leg
		toenail arsenic concentration, µg/kg Exp. Level n adjOR (CI) continuous NR 2.03 n/a Stat Method: multivariate regression; ordered logistic regression models
		toenail arsenic concentration, µg/kg Exp. Level n regr (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		coeff continuous NR 0.0597 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, right arm
		toenail arsenic concentration, µg/kg Exp. Level n adjOR (CI) continuous NR 1.71 n/a Stat Method: multivariate regression; ordered logistic regression models
		toenail arsenic concentration, µg/kg Exp. Level n regr coeff (CI) continuous NR 0.0454 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, right leg
		toenail arsenic concentration, µg/kg Exp. Level n adjOR (CI) continuous NR 2.28 n/a Stat Method: multivariate regression; ordered logistic regression models
		toenail arsenic concentration, µg/kg Exp. Level n regr coeff (CI) continuous NR 0.0694 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: vibration threshold, non-dominant hand, fifth digit
		toenail arsenic concentration, µg/kg Exp. Level n adjR2 (CI) continuous NR 0.12 n/a Stat Method: multivariate regression
		Outcome: vibration threshold, non-dominant hand, second digit
		toenail arsenic concentration, µg/kg Exp. Level n adjR2 (CI) continuous NR 0.11 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multivariate regression
	Exposure Surrogate: urine **Exposure Description:** urine samples collected on 3 consecutive days and analyzed for arsenic species; total urinary arsenic (As[III] As[V], MMA, DMA), inorganic arsenic (As[III], As[V]), organic arsenic (MMA, DMA), and arsenite (As[III]) calculated as average of measurements in 3 samples **Population-Level Exposure:** 374.85 µg/L mean 350.01SD	**Outcome: pinprick score, left arm** ***urinary inorganic arsenic concentration, µg/L*** Exp. Level n regr coeff (CI) continuous NR 0.0056 n/a Stat Method: multivariate regression
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 1.88 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, left leg
		urinary inorganic arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 0.00738 n/a Stat Method: multivariate regression
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 2.29 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, right arm
		urinary inorganic arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 0.00458 n/a Stat Method: multivariate regression
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 1.67 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: pinprick score, right leg
		urinary inorganic arsenic concentration, µg/L Exp. Level n regr coeff (CI) continuous NR 0.00844 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multivariate regression
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjOR (CI) continuous NR 2.58 n/a Stat Method: multivariate regression; ordered logistic regression models
		Outcome: vibration threshold, dominant hand, fifth digit
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjR2 (CI) continuous NR 0.12 n/a Stat Method: multivariate regression
		Outcome: vibration threshold, dominant hand, second digit
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjR2 (CI) continuous NR 0.13 n/a Stat Method: multivariate regression
		Outcome: vibration threshold, non-dominant hand, fifth digit
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjR2 (CI) continuous NR 0.13 n/a Stat Method: multivariate regression
		Outcome: vibration threshold, non-dominant hand, second digit
		urinary inorganic arsenic concentration, µg/L Exp. Level n adjR2 (CI) continuous NR 0.13 n/a Stat Method: multivariate regression
Park et al. (2014) **Study Type:** case-control **Location:** Korea, Republic Of region not available	**Exposure Surrogate:** serum **Exposure Description:** nonfasting blood samples were collected and serum extracted; analytical methods were validated using certified reference material **Population-Level Exposure:**	**Outcome: Alzheimer's disease (AD)** ***arsenic concentration in serum by Alzheimer's Disease status, µg/L*** Exp. Level n mean (CI) controls 67 28.66 n/a cases 64 28.08 n/a Stat Method: t-test

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Population: elderly patients with probable Alzheimer's Disease n cases: 89 n control: 118	28.37 µg/L mean	
Paul et al. (2013) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** male and female adult residents with skin lesions from 3 villages with high arsenic concentrations n cases: 189 n control: 171	**Exposure Surrogate:** drinking water **Exposure Description:** samples collected directly from study participants during 2005-2006 and 2010-2011 study periods **Population-Level Exposure:** mean concentration in drinking water ranged from 3.7 (unexposed) to 190.1 (exposed) in both analyses	**Outcome: conjunctival irritations** ***drinking water arsenic concentration by exposure status and year, unitless*** Exp. Level / n / OR / (CI) unexposed (2005-2006 analysis) / NR / 1 / n/a unexposed (2010-2011 analysis) / NR / 1 / n/a exposed (2005-2006 analysis) / NR / 11.15 / 4.91, 25.32 exposed (2010-2011 analysis) / NR / 20.51 / 9.84, 42.72 Stat Method: OR with 95% CI; 2005 - 2006 data compared to 2010 - 2011 data using Chi-Square test **Outcome: peripheral neuropathy** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / OR / (CI) unexposed (2005-2006 analysis) / NR / 1 / n/a unexposed (2010-2011 analysis) / NR / 1 / n/a exposed (2005-2006 analysis) / NR / 9.08 / 3.48, 23.72 exposed (2010-2011 analysis) / NR / 18.48 / 7.75, 44.06 Stat Method: OR with 95% CI; 2005 - 2006 data compared to 2010 - 2011 data using Chi-Square test

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Rosado et al. (2007) Study Type: cross-sectional Location: Mexico (Torreon) Population: children 6-8 years of age attending school near a metallurgic smelter complex n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urine samples collected the morning after subjects fasted overnight; urinary arsenic concentrations include inorganic As, monomethylarsenic, dimethylarsenic, and the sum of all metabolic species of arsenic **Population-Level Exposure:** 58.1 µg/dL mean 33.2SD	**Outcome: attention: letter sequencing** ***urinary arsenic, µg/dL*** Exp. Level: continuous in children with UAs <50 µg/L; n: NR; adjOR: 0.992; (CI): 0.963, 1.021 Exp. Level: continuous in children with UAs >50 µg/L; n: NR; adjOR: 0.993; (CI): 0.988, 0.999 Stat Method: multiple linear regression
		Outcome: attention: visual search ***urinary arsenic, µg/dL*** Exp. Level: continuous in children with UAs <50 µg/L; n: NR; adjBeta: -0.008; (CI): -0.022, 0.005 Exp. Level: continuous in children with UAs >50 µg/L; n: NR; adjBeta: -0.006; (CI): -0.012, 0 Stat Method: multiple linear regression
		Outcome: attention: WISC-RM coding subscale ***urinary arsenic, µg/dL*** arsenic not significantly associated with attention: WISC-RM Coding Subscale
		Outcome: memory: Sternberg memory ***urinary arsenic, µg/dL*** Exp. Level: continuous in; n: NR; adjBeta: -0.027; (CI): -0.053, -0.002

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		children with UAs <50 µg/L: NR; 0.002; -0.008, 0.012 Continuous in children with UAs >50 µg/L Stat Method: multiple linear regression
		Outcome: memory: stimulus discrimination ***urinary arsenic, µg/dL*** Exp. Level: continuous in children with UAs <50 µg/L; n: NR; adjOR: 0.982; (CI): 0.957, 1.008 Continuous in children with UAs >50 µg/L; n: NR; adjOR: 1.004; (CI): 1.000, 1.008 Stat Method: multiple linear regression
		Outcome: memory: visual memory span ***urinary arsenic, µg/dL*** Exp. Level: continuous in children with UAs <50 µg/L; n: NR; adjBeta: -0.003; (CI): -0.007, 0.000 continuous in children with UAs >50 µg/L; n: NR; adjBeta: -0.001; (CI): -0.002, 0.003 Stat Method: multiple linear regression
		Outcome: memory: WISC-RM digit span subscale ***urinary arsenic, µg/dL*** Exp. Level | n | adjBeta | (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects					
Reference and Study Design	**Exposure Measures**	**Results**			
		continuous in children with UAs <50 µg/L	NR	-0.037	-0.065, -0.010
		continuous in children with UAs >50 µg/L	NR	-0.012	-0.037, 0.012
		Stat Method: multiple linear regression			
		Outcome: problem solving and vocabulary: math achievement test			
		urinary arsenic, µg/dL arsenic not significantly associated with problem solving and vocabulary: math achievement test in children with urinary arsenic >50 µg/L, but significantly reduced in children with urinary arsenic <50 µg/L			
		Outcome: problem solving and vocabulary: Peabody picture vocabulary test			
		urinary arsenic, µg/dL			
		Exp. Level	n	adjBeta	(CI)
		continuous in children with UAs <50 µg/L	NR	-0.185	-0.293, -0.078
		continuous in children with UAs >50 µg/L	NR	-0.058	-0.120, 0.004
		Stat Method: multiple linear regression			
		Outcome: problem solving and vocabulary: visual-spatial abilities with figure design			
		urinary arsenic, µg/dL			
		Exp. Level	n	adjBeta	(CI)
		continuous in children	NR	-0.018	-0.096, 0.061

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		with UAs <50 µg/L continuous in children with UAs >50 µg/L | NR | -0.028 | -0.053, -0.004 Stat Method: multiple linear regression
		Outcome: problem solving and vocabulary: WISC-RM arithmetic subscale
		urinary arsenic, µg/dL arsenic not significantly associated with problem solving and vocabulary: WISC-RM arithmetic subscale
	Exposure Surrogate: urine **Exposure Description:** urine samples collected the morning after subjects fasted overnight; urinary arsenic concentrations include inorganic As, monomethylarsenic, dimethylarsenic, and the sum of all metabolic species of arsenic **Population-Level Exposure:** 58.1 µg/dL mean 33.2SD	**Outcome: attention: letter sequencing**
		urinary arsenic (overall group), µg/dL Exp. Level | n | adjOR | (CI) continuous | NR | 0.992 | 0.987, 0.996 Stat Method: multiple linear regression
		Outcome: attention: visual search
		urinary arsenic (overall group), µg/dL Exp. Level | n | adjBeta | (CI) continuous | NR | -0.007 | -0.011, -0.002 Stat Method: multiple linear regression
		Outcome: memory: Sternberg memory
		urinary arsenic (overall group), µg/dL Exp. Level | n | adjBeta | (CI) continuous | NR | -0.002 | -0.007, 0.004

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multiple linear regression
		Outcome: memory: stimulus discrimination ***urinary arsenic (overall group), µg/dL*** Exp. Level: continuous; n: NR; adjOR: 0.998; (CI): 0.993, 1.004 Stat Method: multiple linear regression
		Outcome: memory: visual memory span ***urinary arsenic (overall group), µg/dL*** Exp. Level: continuous; n: NR; adjBeta: 0; (CI): -0.002, 0.001 Stat Method: multiple linear regression
		Outcome: memory: WISC-RM digit span subscale ***urinary arsenic (overall group), µg/dL*** Exp. Level: continuous; n: NR; adjBeta: -0.014; (CI): -0.025, -0.002 Stat Method: multiple linear regression
		Outcome: problem solving and vocabulary: Peabody picture vocabulary test ***urinary arsenic (overall group), µg/dL*** Exp. Level: continuous; n: NR; adjBeta: -0.064; (CI): -0.115, -0.013 Stat Method: multiple linear regression
		Outcome: problem solving and vocabulary: visual-spatial abilities with figure design ***urinary arsenic (overall group), µg/dL*** Exp. Level: continuous; n: NR; adjBeta: -0.024; (CI): -0.045, -0.004 Stat Method: multiple linear regression

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
See et al. (2007) **Study Type:** cross-sectional **Location:** Taiwan (Putai Township of Chiayi County) **Population:** adult residents in arseniasis-hyperendemic villages who previously consumed artesian well water n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure derived by multiplying the arsenic concentration in artesian well water from levels measured in 1960s by the self-reported duration of water consumption; subjects who moved were categorized as having unknown exposure levels **Population-Level Exposure:** 0-20 mg/L - yr range	**Outcome: eye: cortical opacity** ***cumulative arsenic drinking water exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / 12 / 1 / n/a 0.1-12.0 / 9 / 0.74 / 0.25, 2.18 12.1-20.0 / 24 / 1.36 / 0.51, 3.65 >20.0 / 37 / 1.25 / 0.42, 3.69 Unknown / 37 / 2.1 / 0.75, 5.87 Stat Method: chi-square test ***cumulative arsenic drinking water exposure, mg/L - yr*** Exp. Level / n / OR / (CI) 0 / 12 / 1 / n/a 0.1-12.0 / 9 / 0.66 / 0.26, 1.69 12.1-20.0 / 24 / 2.5 / 1.11, 5.61 >20.0 / 37 / 6.42 / 2.85, 14.48 Unknown / 37 / 4.53 / 2.07, 9.93 Stat Method: chi-square test **Outcome: eye: nuclear opacity** ***cumulative arsenic drinking water exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0 / 8 / 1 / n/a 0.1-12.0 / 4 / 0.65 / 0.16, 2.62 12.1-20.0 / 19 / 1.79 / 0.57, 5.58 >20.0 / 28 / 1.74 / 0.51, 5.90 Unknown / 23 / 2.03 / 0.59, 7.01 Stat Method: chi-square test ***cumulative arsenic drinking water exposure, mg/L - yr*** Exp. Level / n / OR / (CI) 0 / 8 / 1 / n/a 0.1-12.0 / 4 / 0.44 / 0.13, 1.54 12.1-20.0 / 19 / 2.97 / 1.18, 7.48 >20.0 / 28 / 7.29 / 2.89, 18.38 Unknown / 23 / 4.23 / 1.69, 10.56 Stat Method: chi-square test **Outcome: eye: overall cataract** ***cumulative arsenic drinking water exposure, mg/L - yr***

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjOR / (CI) 0 / 15 / 1 / n/a 0.1-12.0 / 12 / 1.08 / 0.39, 2.97 12.1-20.0 / 31 / 2.27 / 0.90, 5.72 >20.0 / 43 / 2.19 / 0.81, 5.91 Unknown / 43 / 2.7 / 0.99, 7.29 Stat Method: chi-square test
		cumulative arsenic drinking water exposure, mg/L - yr Exp. Level / n / OR / (CI) 0 / 15 / 1 / n/a 0.1-12.0 / 12 / 0.71 / 0.30, 1.64 12.1-20.0 / 31 / 2.58 / 1.23, 5.43 >20.0 / 43 / 5.97 / 2.78, 12.80 Unknown / 43 / 4.22 / 2.02, 8.76 Stat Method: chi-square test
		Outcome: eye: posterior subcapsular opacity
		cumulative arsenic drinking water exposure, mg/L - yr Exp. Level / n / adjOR / (CI) 0 / 5 / 1 / n/a 0.1-12.0 / 5 / 2.19 / 0.4, 12.07 12.1-20.0 / 15 / 4.78 / 1.03, 22.18 >20.0 / 28 / 5.7 / 1.23, 26.32 Unknown / 22 / 4.1 / 0.84, 19.94 Stat Method: chi-square tes
		cumulative arsenic drinking water exposure, mg/L - yr Exp. Level / n / OR / (CI) 0 / 5 / 1 / n/a 0.1-12.0 / 5 / 0.88 / 0.24, 3.21 12.1-20.0 / 15 / 3.75 / 1.26, 11.2 >20.0 / 28 / 25.1 / 4.01, 33.97 Unknown / 22 / 6.47 / 2.23, 18.76 Stat Method: chi-square test
Tseng et al. (2006) **Study Type:** cross-sectional **Location:** Taiwan	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic exposure based on previously conducted large-scale study; arsenic exposure indices based on well water samples from each	**Outcome: Sural Sensory Action Potential (SAP) nerve conduction velocity (NCV) in m/s**
		arsenic concentration in well water, µg/L Exp. Level / n / adjOR / (CI) ≤ 10 / NR / 1 / n/a 10.0-50.0 / NR / 0.9 / 0.3, 3.2 >50 / NR / 2.4 / 0.7, 8.1

Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(Langyang Basin) **Population:** adolescent students with arsenic contaminated drinking water n cases: 117 n control: n/a	participant's household; cumulative arsenic dose calculated based on volume consumed and self-reported years of consumption; 3,901 wells were matched to students using questionnaire **Population-Level Exposure:** 0.15-3.59 µg/L range	Stat Method: multiple logistic regression ***cumulative dose of arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 50.0 / NR / 1 / n/a 50.1-100 / NR / 0.4 / 0.04, 3.2 >100 / NR / 2.9 / 1.1, 7.5 Stat Method: multiple logistic regression ***length of time (years) since stopping arsenic exposure, µg/L*** Exp. Level / n / adjOR / (CI) >1 / NR / 1 / n/a 0-1 / NR / 0.6 / 0.2, 1.7 0 / NR / 1.3 / 0.4, 4.7 Stat Method: multiple logistic regression

--: not reported; n: number of cases (when presented in Results column)

5.11.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Nervous System Effects

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5.12 Summary of Observational Epidemiology Studies for Health Effect Category: Other

Summary of Observational Epidemiology Studies for Health Effect Category: Other		
Reference and Study Design	**Exposure Measures**	**Results**
Chung et al. (2012) **Study Type:** cohort (prospective) **Location:** Taiwan (Homei, Fuhsin, Hsinming) **Population:** residents of arseniasis-endemic areas n total: 1563	**Exposure Surrogate:** drinking water **Exposure Description:** information on median arsenic level in artesian well water of each village acquired from previous studies carried out in the early 1960s (Lai et al., 1994); some study subjects had moved from one village to another, and there were differences in arsenic concentrations between villages **Population-Level Exposure:** 0.7-0.93 mg/L range	**Outcome: all site cancers** ***average water arsenic concentration (tertiles), mg/L*** not significant for average urinary arsenic or cumulative arsenic exposure in drinking water; for arsenic profiles, only significant trend for inorganic arsenic% (not %MMA or %DMA)
Hsu et al. (2013b) **Study Type:** cohort (prospective) **Location:** Taiwan (SW: Peimen, Hsuechia, Ichu, and Putai Townships; NE: Chiaohsi, Chuangwei, Wuchieh, and Tungshan Townships) **Population:** residents of an arseniasis-endemic area with skin lesions n total: 9525	**Exposure Surrogate:** drinking water **Exposure Description:** SW population: median arsenic level of several wells shared in a village derived from two surveys; NE population: arsenic level of well water samples collected during home interviews **Population-Level Exposure:** 10-500 µg/L range	**Outcome: all internal cancers** ***arsenic concentration in well water (non-diabetes mellitus vs. diabetes mellitus subjects), µg/L*** Exp. Level / n / HR / (CI) non-DM w/ As <500 — NR — 1 — n/a DM w/ As <500 — NR — 1.45 — 0.24, 1.70 non-DM w/ As ≥ 500 — NR — 1 — n/a DM w/ As ≥ 500 — NR — 1.72 — 1.33, 2.22 Stat Method: Cox regression analysis with time-dependent DM status
Majumdar et al. (2009) **Study Type:** cross-sectional	**Exposure Surrogate:** drinking water **Exposure Description:** for each participant, water samples from private	**Outcome: weakness and diarrhea** ***arsenic concentration in drinking water (males), µg/L*** significant increase in weakness and diarrhea in

Summary of Observational Epidemiology Studies for Health Effect Category: Other		
Reference and Study Design	**Exposure Measures**	**Results**
Location: India (West Bengal) **Population:** residents of arsenic-affected villages n cases: 3825 n control: 3451	or public tube wells analyzed for arsenic; exposure categories developed based on arsenic levels **Population-Level Exposure:** 50-500 µg/L range	males and females exposed to >500 µg/L
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho) **Population:** adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	**Outcome: all cancers** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 / 11 / 0.78 / 0.41, 1.41 0.05-0.99 / 5 / 1.3 / 0.51, 3.06 ≥ 1 / 18 / 3.63 / 2.25, 5.71 Stat Method: Cox proportional hazard

--: not reported; n: number of cases (when presented in Results column)

5.12.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Other

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5.13 Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults) n exposed: 56,378 n total: 57053	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** not available	**Outcome: kidney cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 0.94 / 0.84, 1.06 Stat Method: Cox regression
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** 0.7 µg/L median	**Outcome: kidney cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 0.89 / 0.65, 1.22 Stat Method: Cox regression
Chen et al. (2011a) **Study Type:** cross-sectional **Location:** Taiwan (Changhua County	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration measured from spot sample for each individual; results below LOD assigned one-half of LOD	**Outcome: renal tubular dysfunction (estimated glomerular filtration rate <60 mL/min)** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) =<35 / NR / 1 / n/a >35-75 / NR / 1.11 / 0.56, 1.80 >75-200 / NR / 0.68 / 0.42, 1.33 >200 / NR / 1.98 / 0.95, 4.99

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(central Taiwan)) **Population:** adult residents of village with history of higher than average arsenic in drinking water n cases: 910 n control: 133	**Population-Level Exposure:** 85.13 µg/g-creatinine median	Stat Method: multivariate logistic regression **Outcome: renal tubular dysfunction (estimated glomerular filtration rate <90 mL/min)** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) =<35 / NR / 1 / n/a >35-75 / NR / 1.45 / 0.49, 1.88 >75-200 / NR / 2.15 / 1.06, 3.78 >200 / NR / 2.16 / 1.11, 3.49 Stat Method: multivariate logistic regression **Outcome: renal tubular dysfunction (urinary beta2 microglobulin >0.154 mg/L)** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) =<35 / NR / 1 / n/a >35-75 / NR / 1.69 / 0.94, 3.64 >75-200 / NR / 2.11 / 1.23, 4.98 >200 / NR / 2.04 / 1.11, 4.37 Stat Method: multivariate logistic regression
Chiou et al. (2005) **Study Type:** cohort (retrospective) **Location:** Taiwan (southwestern: Tainan County (Yenshui, Beimen, and Shuechia townships), Chiayi County (Putai and Yichu townships)) **Population:** adults and children living in arseniasis-endemic townships n total: 28499	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration as reported by the National Taiwan University Group; median concentration used as surrogate if village had multiple wells **Population-Level Exposure:** 0.1-0.6 mg/L range	**Outcome: Renal disease** ***drinking water arsenic concentration - renal disease, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.898 / n/a Stat Method: Logistic regression model ***drinking water arsenic concentration - non-diabetic subjects, mg/L*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-0.29 / NR / 1.17 / 0.75, 1.83 0.3-0.59 / NR / 0.78 / 0.48, 1.24 ≥ 0.6 / NR / 1.3 / 0.85, 2.00 Stat Method: Stratified analysis and unconditional logistic regression ***drinking water arsenic concentration - Type 2 diabetic subjects, mg/L*** Exp. Level / n / adjOR / (CI) <0.1 / NR / 1 / n/a 0.1-0.29 / NR / 0.69 / 0.27, 1.81 0.3-0.59 / NR / 1.33 / 0.67, 2.63 ≥ 0.6 / NR / 2.08 / 1.05, 4.11

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: Stratified analysis and unconditional logistic regression
Ferreccio et al. (2013a) **Study Type:** case-control **Location:** Chile (Regions I and II in northern Chile) **Population:** residents with kidney cancer in area formerly having arsenic-contaminated drinking water n cases: 122 n control: 640	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic intake calculated by multiplying each average daily arsenic intake by 365 days/year and summing the results of all years; exposures in the 5 years preceding cancer diagnosis or control identification not included **Population-Level Exposure:** 10.3 mg mean	**Outcome: renal pelvis and ureter cancers (transitional cell carcinomas)** ***cumulative arsenic exposure, mg*** Exp. Level / n / adjOR / (CI) <10 / 7 / 1 / n/a 10-25 / 12 / 5.49 / 2.02, 14.88 >25 / 5 / 10.35 / 2.57, 41.64 Stat Method: unconditional logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** historical concentrations of arsenic in drinking water available for Northern Chile (1930-1995 onward); arsenic concentrations in 1958-1970 averaged 860 µg/L; installation of a treatment plant reduced recent concentrations to <10 µg/L; exposure categories based on arsenic intake in the 3 main exposure areas of Arica/Iquique, Calama, and Antofagasta **Population-Level Exposure:** 0-1000 µg/day range	**Outcome: other/unclassified kidney cancers** ***arsenic concentration in drinking water, µg/day*** arsenic not associated with other/unclassified kidney cancers **Outcome: renal cell cancers** ***arsenic concentration in drinking water, µg/day*** arsenic not significantly associated with renal cell cancers **Outcome: renal pelvis and ureter cancers (transitional cell carcinomas)** ***highest 5-year daily average arsenic intake, µg/day*** Exp. Level / n / adjOR / (CI) <400 / 5 / 1 / n/a 400-1,000 / 8 / 5.71 / 1.65, 19.82 >1,000 / 11 / 11.09 / 3.60, 34.16 Stat Method: unconditional logistic regression ***highest daily arsenic intake before 1971, µg/day*** Exp. Level / n / adjOR / (CI) <400 / 7 / 1 / n/a 400-1,000 / 6 / 3.36 / 1.02, 11.10 >1,000 / 11 / 7.13 / 2.61, 19.44 Stat Method: unconditional logistic regression
García-Esquinas et al. (2013)	**Exposure Surrogate:** urine **Exposure Description:** individual urine	**Outcome: kidney cancer** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th / NR / 0.44 / 0.14, 1.40

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cohort (prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	samples collected and analyzed for arsenic speciation **Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	percentiles Stat Method: Cox proportional hazard models; log transformed
Hawkesworth et al. (2013) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** children in Maternal and Infant Nutrition Interventions in Matlab (MINIMat) cohort n total: 2499	**Exposure Surrogate:** maternal urine **Exposure Description:** spot urine samples from participating women collected at 8 and 30 weeks gestation; log transformed as continuous variable for analysis; median maternal urinary arsenic was 80 µg/L (10th, 90th percentile: 24, 383 µg/L) at week 8 of gestation and 83 µg/L (10th, 90th: 26, 415 µg/L) at week 30 **Population-Level Exposure:** 80 mg/L median	**Outcome: glomerular filtration** ***maternal urinary arsenic concentration (combined), mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -14.2 / -32.2, 3.7 Stat Method: linear regression ***maternal urinary arsenic concentration week 30, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.51 / -16.2, 17.2 Stat Method: linear regression ***maternal urinary arsenic concentration week 8, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -21.2 / -39.2, -3.2 Stat Method: linear regression **Outcome: kidney volume** ***maternal urinary arsenic concentration (combined), mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 2.89 / -6.17, 11.96 Stat Method: linear regression ***maternal urinary arsenic concentration week 30, mg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 6.04 / -3.11, 15.2 Stat Method: linear regression ***maternal urinary arsenic concentration week 8, mg/L*** Exp. Level / n / adjBeta / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		continuous NR 0.75 -8.59, 10.08 Stat Method: linear regression
	Exposure Surrogate: urine **Exposure Description:** urine samples collected from participating children at 18 months of age; log transformed as continuous variable for analysis **Population-Level Exposure:** 34 mg/L median	**Outcome: glomerular filtration** ***infant urinary arsenic concentration 18 months, mg/L*** Exp. Level / n / adjBeta / (CI) continuous NR -33.4 -70.2, 3.34 Stat Method: linear regression **Outcome: kidney volume** ***infant urinary arsenic concentration 18 months, mg/L*** Exp. Level / n / adjBeta / (CI) continuous NR -1.9 -23.45, 27.26 Stat Method: linear regression
Huang et al. (2011) **Study Type:** case-control **Location:** Taiwan region not available **Population:** adults with and without renal cell carcinoma in region without obvious sources of arsenic exposure n cases: 132 n control: 260	**Exposure Surrogate:** urine **Exposure Description:** total concentration of arsenic in daytime urine sample based on sum of individual arsenic species measured; mean urinary total arsenic for cases and controls: 25.16 (+/- 2.22) and 21.15 (+/- 1.02) µg/L, respectively **Population-Level Exposure:** not available	**Outcome: renal cell carcinoma** ***total urinary arsenic concentration, µg/g-creatinine*** Total urinary arsenic level was significantly associated with risk of developing renal cell carcinomas in a dose-reponse relationship after multivariate adjustment
Huang et al. (2012) **Study Type:** case-control **Location:** Taiwan region not available **Population:** adults with and without renal cell	**Exposure Surrogate:** urine **Exposure Description:** total concentration of arsenic in daytime urine sample based on sum of individual arsenic species measured **Population-Level Exposure:** 12.3-20.95 µg/g-creatinine range	**Outcome: renal cell carcinoma** ***total urinary arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjOR / (CI) ≤ 12.30 32 1 n/a 12.30-20.95 44 1.43 0.73, 2.79 >20.95 56 2.62 1.32, 5.22 Stat Method: multiple logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
carcinoma in region without obvious sources of arsenic exposure n cases: 132 n control: 245		
Kurttio et al. (1999) **Study Type:** case-control **Location:** Finland region not available **Population:** register-based cohort of Finnish people living outside municipal water system from 1967-1980; 61 bladder cancer cases, 49 kidney cancer cases n cases: 49 n control: 275	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration measured in well-water samples collected Jul-Nov 1996 from locations where individuals lived from 1967-1980 **Population-Level Exposure:** not available	**Outcome: kidney cancer** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjRR / (CI) <.1 / NR / 1 / n/a 0.1-0.5 / NR / 0.78 / 0.37, 1.66 ≥ 0.5 / NR / 1.49 / 0.67, 3.31 Stat Method: Linear modeling after log transformation
	Exposure Surrogate: drinking water **Exposure Description:** cumulative arsenic dose calculated based on duration of exposure as reported in questionnaire and sampled arsenic concentration in well water; if questionnaire data not available, assumed mean value from the reference cohort for consumption; arsenic concentration in drinking water before and after well-water use was considered null **Population-Level Exposure:** 0.8 mg median	**Outcome: kidney cancer** ***cumulative arsenic dose, mg*** Exp. Level / n / adjRR / (CI) <0.5 / NR / 1 / n/a 0.5-2.0 / NR / 0.74 / 0.33, 1.68 ≥ 2.0 / NR / 0.8 / 0.42, 1.86 Stat Method: Linear modeling after log transformation
	Exposure Surrogate: drinking water **Exposure Description:** daily dose of arsenic estimated from sampled arsenic concentration in well water (collected and measured 1996 from locations where individuals lived from 1967-1980) and reported consumption of well water from the 1970s; if questionnaire data not available assumed mean value from the reference cohort for consumption; arsenic concentration in drinking water	**Outcome: kidney cancer** ***daily dose of arsenic, µg/day*** Exp. Level / n / adjRR / (CI) <0.2 / NR / 1 / n/a 0.2-1.0 / NR / 1.08 / 0.52, 2.25 ≥ 1.0 / NR / 1.21 / 0.52, 2.82 Stat Method: Linear modeling after log transformation

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	before and after well-water use considered null **Population-Level Exposure:** 0.2 µg/day median	
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2203 n total: 2203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: kidney cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 2.36 / n/a 1000-4999 / NR / 1.32 / n/a ≥ 5000 / NR / 1.13 / n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 2.51 / n/a 1000-4999 / NR / 1.13 / n/a ≥ 5000 / NR / 1.43 / n/a Stat Method: standardized mortality ratios **Outcome: nephritis and nephrosis** ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 2.02 / n/a 1000-4999 / NR / 2.1 / n/a ≥ 5000 / NR / 0.88 / n/a Stat Method: standardized mortality ratio; OCMAP adapted to nonoccupational cohort
Mostafa and Cherry (2013) **Study Type:** case-control **Location:** Bangladesh (Dhaka) **Population:** patients from a single clinic in a rural high arsenic area who developed renal cancer	**Exposure Surrogate:** drinking water **Exposure Description:** 3534 wells sampled by British Geological Survey; arsenic in drinking water estimated for each subject as mean arsenic concentration (non-detects set at 0.5 µg/L) in wells for the area in which the patient lived at the time of biopsy; where address as extracted did not indicate the area, the clinical record was reviewed and assigned to the correct or closest area **Population-Level Exposure:**	**Outcome: renal cell cancer (RCC)** ***water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <10 / NR / 1 / n/a 10-<50 / NR / 1.37 / 0.92, 2.06 50-<100 / NR / 2.05 / 1.27, 3.32 100-<200 / NR / 2.28 / 1.42, 3.64 200-<300 / NR / 3.95 / 2.42, 6.44 ≥ 300 / NR / 6 / 3.24, 11.12 Stat Method: multilevel logistic model ***well water arsenic concentration (1994 or earlier), µg/L*** Exp. Level / n / adjOR / (CI) <10 / NR / 1 / n/a 10-<50 / NR / 2.47 / 1.52, 4.01

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
n cases: 986 n control: 503	10-300 µg/L range	50-<100 NR 3.52 2.06, 6.01 100-<200 NR 2.89 1.76, 4.783 200-<300 NR 5.4 3.16, 9.23 ≥ 300 NR 9.22 5.07, 16.76 Stat Method: multilevel logistic model
		well water arsenic concentration (1995 or later), µg/L Exp. Level / n / adjOR / (CI) <10 NR 1 n/a 10-<50 NR 0.67 0.34, 1.32 50-<100 NR 0.79 0.30, 2.05 100-<200 NR 2.5 0.77, 8.11 200-<300 NR 2.86 1.12, 7.30 ≥ 300 NR 2.67 0.46, 13.39 Stat Method: multilevel logistic model
		Outcome: renal cell cancer (RCC) and transitional cell cancer (TCC)
		water arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) <10 NR 1 n/a 10-<50 NR 1.29 0.86, 1.91 50-<100 NR 2.12 1.33, 3.39 100-<200 NR 2.41 1.53, 3.81 200-<300 NR 3.84 2.38, 6.19 ≥ 300 NR 6 3.29, 10.98 Stat Method: multilevel logistic model
		Outcome: transitional cell cancer (TCC)
		water arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) <10 NR 1 n/a 10-<50 NR 0.51 0.16, 1.63 50-<100 NR 4.59 1.70, 12.36 100-<200 NR 4.94 1.88, 12.99 200-<300 NR 4.83 1.77, 13.13 ≥ 300 NR 7.7 2.37, 25.03 Stat Method: multilevel logistic model
Sawada et al. (2013) **Study Type:** cohort (prospective)	**Exposure Surrogate:** diet **Exposure Description:** detailed questionnaire on food intake/frequency;	**Outcome: kidney cancer**
		inorganic arsenic intake (females; quartiles), µg/day Exp. Level / n / HR / (CI) 40.6 13 1 n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Location: Japan (Iwate, Akita, Nagano, Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90378	average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	53.7 7 0.48 0.19, 1.23 62.6 5 0.34 0.12, 0.96 105.7 9 0.64 0.27, 1.53 Stat Method: Multivariate regression ***inorganic arsenic intake (males; quartiles), µg/day*** Exp. Level n HR (CI) 40.5 14 1 n/a 54.7 22 1.72 0.87, 3.39 63.5 21 1.66 0.83, 3.35 99.1 26 2.05 1.05, 4.03 Stat Method: Multivariate regression
Yuan et al. (2010) **Study Type:** cohort (retrospective) **Location:** Chile (Region II (Mejillones and Antofagasta)) **Population:** residents of areas with high arsenic concentrations in water number of subjects not reported	**Exposure Surrogate:** residency **Exposure Description:** based on measurements of drinking water in Antofagasta and Mejillones 1950 - 1970 defined as the high exposure period, so individuals born during this period would have had exposure in utero and in early childhood, but individuals born before would only have early childhood exposure **Population-Level Exposure:** 60-870 range	**Outcome: kidney cancer mortality** ***arsenic exposure by birth year (combined), units not available*** Exp. Level n SMR (CI) born 1950 - 1970 8 7.08 3.05, 14 born before 1950 187 3.12 2.69, 3.61 Stat Method: Poisson regression ***arsenic exposure by birth year (men only), units not available*** Exp. Level n SMR (CI) born 1950 - 1970 4 5.63 1.52, 14.4 born before 1950 103 2.68 2.19, 3.26 Stat Method: Poisson regression ***arsenic exposure by birth year (women only), units not available*** Exp. Level n SMR (CI) born 1950 - 1970 4 9.52 2.56, 24.4 born before 1950 84 3.91 3.12, 4.84 Stat Method: Poisson regression

--: not reported; n: number of cases (when presented in Results column)

5.13.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Renal Effects

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5.14Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Reference and Study Design	Exposure Measures	Results
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults) n exposed: 56,378 n total: 57053	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** not available	**Outcome: breast cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 1 / 0.99, 1.02 Stat Method: Cox regression **Outcome: prostate cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 1 / 0.99, 1.03 Stat Method: Cox regression
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** 0.7 µg/L median	**Outcome: breast cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 1.03 / 0.99, 1.08 Stat Method: Cox regression **Outcome: prostate cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 1.03 / 0.97, 1.09 Stat Method: Cox regression
García-Esquinas et al. (2013) **Study Type:** cohort (prospective)	**Exposure Surrogate:** urine **Exposure Description:** individual urine samples collected and analyzed for arsenic speciation	**Outcome: breast cancer** ***urinary arsenic concentration, µg/g-creatinine*** no significant association between arsenic and breast cancer **Outcome: prostate cancer**

Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Reference and Study Design	Exposure Measures	Results
Location: United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	**Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th percentiles / 18 / 3.3 / 1.28, 8.48 Stat Method: Cox proportional hazard models; log transformed
Garland et al. (1996) **Study Type:** case-control (nested) **Location:** United States (11 States) **Population:** Nurses' Health Study cohort members with no prior history of of cancer in 1982 n cases: 427 n control: 450	**Exposure Surrogate:** toenails **Exposure Description:** case-control pair samples analyzed together; 47 samples below LOD and set to the value of LOD; concentrations log € transformed and regressed (adjusted) for weight by laboratory batch; exposure quintiles derived based on distribution in controls **Population-Level Exposure:** 0.12 µg/g mean	**Outcome: breast cancer** ***toenail arsenic concentration (quintiles), µg/g*** Exp. Level / n / adjOR / (CI) <0.059 / 54 / 1 / n/a 0.059-0.078 / 67 / 1.19 / 0.71, 1.98 0.079-0.103 / 56 / 1.01 / 0.59, 1.73 0.104-0.138 / 62 / 1.12 / 0.67, 1.90 >0.138 / 69 / 1.12 / 0.66, 1.91 Stat Method: unconditional multivariate logistic regression
Kwok et al. (2006) **Study Type:** cross-sectional **Location:** Bangladesh (Faridpur district (Faridpur Sadar upazila) and Chandpur district (Matlab and Shahrasti upazilas)) **Population:** residents of 261 highly arsenic-contaminated villages n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** water samples collected during in-home interview from main drinking water source used during pregnancy **Population-Level Exposure:** 0.5-668 ppb range	**Outcome: stillbirths** ***drinking water arsenic concentration, ppb*** Exp. Level / n / adjOR / (CI) continuous / NR / 0.999 / 0.996, 1.002 Stat Method: multivariate logistic regression ***drinking water arsenic concentration, ppb*** Exp. Level / n / Prev / (CI) ≤ 10 / 8 / 2.5 / n/a 11-50 / 5 / 2.2 / n/a 51-100 / 6 / 2.7 / n/a 101-200 / 14 / 2.8 / n/a 201-300 / 17 / 3.4 / n/a >300 / 3 / 1.3 / n/a Stat Method: prevalence

Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Reference and Study Design	Exposure Measures	Results
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** deceased male and female members of Latter-day Saints church wards n exposed: 2203 n total: 2203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: breast cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 0.64 / n/a 1000-4999 / NR / 0.7 / n/a ≥ 5000 / NR / 0.4 / n/a Stat Method: standardized mortality ratios **Outcome: other female genital organs cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 0.87 / n/a 1000-4999 / NR / 0.71 / n/a ≥ 5000 / NR / 1.09 / n/a Stat Method: standardized mortality ratios **Outcome: prostate cancer** ***cumulative arsenic exposure (males), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 1.07 / n/a 1000-4999 / NR / 1.7 / n/a ≥ 5000 / NR / 1.65 / n/a Stat Method: standardized mortality ratios **Outcome: uterine cancer** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level / n / SMR / (CI) <1000 / NR / 0.42 / n/a 1000-4999 / NR / 0.49 / n/a ≥ 5000 / NR / 0.65 / n/a Stat Method: standardized mortality ratios
Milton et al. (2005) **Study Type:** cross-sectional **Location:** Bangladesh (Comilla, Chandpur, and Chuadanga districts)	**Exposure Surrogate:** drinking water **Exposure Description:** single well-water measurement used to characterize chronic arsenic exposure; arsenic concentrations recorded as zero replaced with 30 µg/L **Population-Level Exposure:** 279 µg/L mean 355SD	**Outcome: spontaneous abortion** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 50 / NR / 1 / n/a >50 / NR / 2.5 / 1.5, 4.3 51-100 / NR / 2.4 / 1.2, 5.1 >100 / NR / 2.5 / 1.5, 4.4 Stat Method: logistic regression analysis **Outcome: stillbirth** ***drinking water arsenic concentration, µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Reference and Study Design	Exposure Measures	Results
Population: women living in study area with ≥ 1 prior pregnancy n cases: n/a n control: n/a		Exp. Level / n / adjOR / (CI) ≤ 50 / 13 / 1 / n/a >50 / 49 / 2.5 / 1.3, 4.9 51-100 / 4 / 1.1 / 0.3, 3.1 >100 / 45 / 2.9 / 1.5, 5.9 Stat Method: logistic regression analysis
Pollack et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (CA; UT) **Population:** adult females in ENDO Study n exposed: 495 n reference: 131 n total: 626	**Exposure Surrogate:** urine **Exposure Description:** blood and urine specimens collected from women upon completion of interview; urine specimens were analyzed for 20 trace elements **Population-Level Exposure:** 4.94-10.84 µg/L range	**Outcome: endometriosis** ***urinary arsenic concentration (operative cohort) by endometriosis status, µg/L*** Exp. Level / n / mean / (CI) controls / 283 / 8.37 / 7.50, 9.33 cases / 190 / 8.37 / 7.41, 9.46 Stat Method: Student's t-test or Wilcoxon nonparametric test for continuous data ***urinary arsenic concentration (population cohort) by endometriosis status, µg/L*** Exp. Level / n / mean / (CI) controls / 113 / 8.69 / 7.26, 10.39 cases / 14 / 7.74 / 4.88, 12.25 Stat Method: Student's t-test or Wilcoxon nonparametric test for continuous data
Rahman et al. (2010) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** pregnant women enrolled in the Maternal and Infant Nutrition Intervention in Matlab study (MINIMat) n total: 1725	**Exposure Surrogate:** urine **Exposure Description:** urine samples collected at ~approx gestation week 8 and gestation week 30; samples adjusted by specific gravity rather than creatinine; urine levels divided into quintiles **Population-Level Exposure:** 38-2019 µg/L range	**Outcome: spontaneous abortion/miscarriage** ***early pregnancy urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / OR / (CI) <33 / 45 / 1 / n/a 33-57 / 57 / 1.28 / 0.85, 1.93 58-121 / 63 / 1.41 / 0.94, 2.11 122-248 / 47 / 1.06 / 0.69, 1.62 249-1253 / 63 / 1.44 / 0.96, 2.15 Stat Method: logistic regression **Outcome: stillbirths** ***average urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <38 / 3 / 1 / n/a 39-67 / 6 / 2.06 / 0.51, 8.38 68-133 / 7 / 2.35 / 0.6, 9.23 134-267 / 10 / 3.41 / 0.92, 12.63 268-2019 / 6 / 2.02 / 0.5, 8.24

Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Reference and Study Design	Exposure Measures	Results
		Stat Method: logistic regression
Sawada et al. (2013) **Study Type:** cohort (prospective) **Location:** Japan (Iwate, Akita, Nagano, Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90378	**Exposure Surrogate:** diet **Exposure Description:** detailed questionnaire on food intake/frequency; average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	**Outcome: breast cancer** ***arsenic concentration in diet, µg/day*** arsenic not significantly associated with breast cancer **Outcome: endometrial cancer** ***arsenic concentration in diet, µg/day*** arsenic not significantly associated with endometrial cancer **Outcome: prostate cancer** ***arsenic concentration in diet, µg/day*** arsenic not significantly associated with prostate cancer
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho) **Population:** adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	**Outcome: uterine cancer** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 / 0 / 0 / 0, 8.01 0.05-0.99 / 0 / 0 / 0, 37.64 ≥ 1 / 2 / 13.47 / 2.37, 48.63 Stat Method: Cox proportional hazard
Von Ehrenstein et al. (2006) **Study Type:** cross-sectional	**Exposure Surrogate:** drinking water **Exposure Description:** water samples collected from tube wells used at least 6 months since first pregnancy; past arsenic concentration measurements used when wells were closed	**Outcome: spontaneous abortion** ***arsenic concentration in drinking water, µg/L*** Exp. Level / n / adjOR / (CI) 0-49 / 21 / 1 / n/a 50-199 / 2 / 0.91 / 0.25, 3.34 ≥ 200 / 5 / 1.01 / 0.38, 2.70 Stat Method: logistic regression based on

Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

Reference and Study Design	Exposure Measures	Results
Location: India (West Bengal) **Population:** women residing in 21 villages of West Bengal, India n cases: n/a n control: n/a	**Population-Level Exposure:** 0-200 µg/L range	method of generalized estimating equations **Outcome: stillbirths** ***arsenic concentration in drinking water, µg/L*** Exp. Level / n / adjOR / (CI) 0-49 / 8 / 1 / n/a 50-199 / 1 / 0.8 / 0.10, 6.66 ≥ 200 / 9 / 6.07 / 1.54, 24.0 Stat Method: logistic regression based on method of generalized estimating equations
Xu et al. (2012) **Study Type:** cross-sectional **Location:** China (Chongqing) **Population:** male patients at infertility clinic n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urine samples collected on same day as semen collection (unless multiple samples given); arsenic concentration dichotomized with cut-offs of the median **Population-Level Exposure:** 4.89 µg/g-creatinine mean 3.67SD	**Outcome: semen volume** ***dichotomised urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) 1 / NR / 1 / n/a 2 / NR / 1.4 / 0.4, 4.8 Stat Method: binary logistic regression **Outcome: sperm concentration** ***dichotomised urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) 1 / NR / 1 / n/a 2 / NR / 0.6 / 0.1, 2.2 Stat Method: binary logistic regression **Outcome: sperm motility** ***dichotomised urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) 1 / NR / 1 / n/a 2 / NR / 1.1 / 0.4, 2.8 Stat Method: binary logistic regression

--: not reported; n: number of cases (when presented in Results column)

5.14.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Reproductive System Effects including Pregnancy Outcomes

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5.15Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults) n exposed: 56,378 n total: 57053	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** not available	**Outcome: lung cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 1 / 0.98, 1.02 Stat Method: Cox regression
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** 0.7 µg/L median	**Outcome: lung cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 0.99 / 0.92, 1.07 Stat Method: Cox regression
Chen et al. (2004a) **Study Type:** cohort (prospective) **Location:** Taiwan (Southwestern coast	**Exposure Surrogate:** drinking water **Exposure Description:** average drinking water arsenic concentrations calculated using median concentration for relevant village wells as measured in the early 1960s (southeastern cohort) or measured concentration for relevant	**Outcome: lung cancer** ***average drinking water arsenic concentration, µg/L*** Exp. Level / n / adjRR / (CI) <10 / 27 / 1 / n/a 10-99 / 31 / 1.09 / 0.63, 1.91 100-299 / 17 / 2.28 / 1.22, 4.27 300-699 / 18 / 3.03 / 1.62, 5.69

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
(Peimen, Hsuehchia, Putai and Ichu townships) and northeaster Lanyang Basin (Tungshan, Chuangwei, Chiaohsi, and Wuchieh townships)) **Population:** adults living in arseniasis-endemic areas, followed from exisiting cohort n total: 10591	personal wells (northeastern cohort) and total years drinking artesian well water; grouped to include enough lung cancer cases in each category **Population-Level Exposure:** 10-700 µg/L range	≥ 700 26 3.29 1.60, 6.78 unknown 20 1.1 0.60, 2.03 Stat Method: Cox proportional hazards regression model
Chen et al. (2010a) **Study Type:** cohort (prospective) **Location:** Taiwan (Lanyang Basin (Tung-Shan, Chuang-Wei, Chiao-His, and Wu-Chieh Townships)) **Population:** adults living in arseniasis-endemic township n total: 6888	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic levels calculated based on arsenic concentration in well water and self-reported years of drinking well water **Population-Level Exposure:** 3523.5 µg/L-year mean 9443.5SD	**Outcome: all lung cancer** ***cumulative arsenic exposure (ref = 0), µg/L-year*** Exp. Level / n / adjRR / (CI) 0 NR 1 n/a <1000 NR 0.56 0.36, 0.89 1000-<5000 NR 0.78 0.5, 1.21 5000-<10,000 NR 1.37 0.8, 2.34 ≥ 10,000 NR 1.52 0.92, 2.52 Stat Method: multivariate regression ***cumulative arsenic exposure (ref = <100), µg/L-year*** Exp. Level / n / adjRR / (CI) <100 43 1 n/a 100-<1000 32 0.65 0.41, 1.02 1000-<5000 51 0.91 0.60, 1.36 5000-<10000 23 1.6 0.96, 2.65 ≥ 10,000 29 1.78 1.11, 2.85 Stat Method: multivariate regression ***cumulative arsenic exposure (ref = <400), µg/L-year*** Exp. Level / n / adjRR / (CI) <400 55 1 n/a 400-<1000 20 0.83 0.50, 1.39 1000-<5000 51 1.06 0.73, 1.56 5000-<10000 23 1.87 1.15, 3.04 ≥ 10,000 29 2.08 1.13, 3.27

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multivariate regression
	Exposure Surrogate: drinking water **Exposure Description:** drinking water arsenic concentration determined from water samples from household wells during home interview **Population-Level Exposure:** 117.2 µg/L mean 297.2SD	**Outcome: adenocarcinoma** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjRR / (CI) <10 / 14 / 1 / n/a 10-49.9 / 20 / 1.5 / 0.76, 2.98 50-99.9 / 4 / 0.7 / 0.23, 2.13 100-299.9 / 6 / 1.06 / 0.41, 2.77 ≥ 300 / 7 / 1.63 / 0.65, 4.05 Stat Method: multivariate regression
		Outcome: all lung cancer ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjRR / (CI) <10 / 48 / 1 / n/a 10-49.9 / 51 / 1.1 / 0.74, 1.63 50-99.9 / 20 / 0.99 / 0.59, 1.68 100-299.9 / 28 / 1.54 / 0.97, 2.46 ≥ 300 / 31 / 2.25 / 1.43, 3.55 Stat Method: multivariate regression
		Outcome: other histological types ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjRR / (CI) <10 / 7 / 1 / n/a 10-49.9 / 11 / 1.7 / 0.66, 4.39 50-99.9 / 3 / 1.1 / 0.28, 4.25 100-299.9 / 5 / 2.03 / 0.64, 6.40 ≥ 300 / 4 / 2.25 / 0.65, 7.71 Stat Method: multivariate regression
		Outcome: small cell carcinoma ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjRR / (CI) <10 / 4 / 1 / n/a 10-49.9 / 8 / 2.02 / 0.61, 6.73 50-99.9 / 0 / NR / n/a 100-299.9 / 4 / 2.77 / 0.69, 11.1 ≥ 300 / 6 / 5.15 / 1.44, 18.4 Stat Method: multivariate regression
		Outcome: squamous cell carcinoma ***drinking water arsenic concentration, µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / adjRR / (CI) <10 / 23 / 1 / n/a 10-49.9 / 12 / 0.53 / 0.26, 1.07 50-99.9 / 13 / 1.32 / 0.67, 2.61 100-299.9 / 13 / 1.52 / 0.77, 3.00 ≥ 300 / 14 / 2.13 / 1.09, 4.17 Stat Method: multivariate regression
Chiou et al. (1995) **Study Type:** cohort (prospective) **Location:** Taiwan (Southwestern coast of Taiwan (Peimen, Hsuechia, Putai, and Ichu townships)) **Population:** BFD patients and healthy residents in arseniasis-endemic townships n exposed: 263 n reference: 2293 n total: 2556	**Exposure Surrogate:** drinking water **Exposure Description:** individual exposure estimated using median arsenic levels in artesian well water in each village combined with residential history information gathered during individual interviews **Population-Level Exposure:** 0.78 mg/L median	**Outcome: lung cancer** ***average arsenic concentration in well water, mg/L*** Exp. Level / n / adjRR / (CI) ≤ 0.05 / 5 / 1 / n/a 0.05-0.70 / 7 / 2.1 / 0.7, 6.8 >0.71 / 7 / 2.7 / 0.7, 10.2 unknown / 10 / 1.5 / 0.5, 4.3 Stat Method: Cox proportional hazards regression analysis
		cumulative water arsenic exposure, mg/L-yr Exp. Level / n / adjRR / (CI) 0 / NR / 1 / n/a 0.1-19.9 / NR / 2.74 / 0.69, 11.0 >20 / NR / 4.01 / 1.0, 16.12 Unknown / NR / 2.01 / 0.55, 7.36 Stat Method: Cox proportional hazards regression analysis
Chung et al. (2012) **Study Type:** cohort (prospective) **Location:** Taiwan (Homei, Fuhsin, Hsinming) **Population:** residents of arseniasis-endemic areas n total: 1563	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure assessment determined by duration of artesian well water use, history or residence, and historical data; cumulative arsenic exposure derived to reflect long-term arsenic exposure by median well water arsenic (population level exposure reported here) x duration of use **Population-Level Exposure:** 9.1-19.5 µg/L-year range	**Outcome: lung cancer** ***cumulative water arsenic exposure (tertiles), µg/L-year*** Exp. Level / n / adjOR / (CI) <9.1 / 10 / 1 / n/a 9.1-19.5 / 13 / 0.9 / 0.39, 2.09 ≥ 19.5 / 34 / 1.47 / 0.66, 3.31 Stat Method: Cox proportional hazard model
	Exposure Surrogate: drinking water	**Outcome: lung cancer** ***average water arsenic concentration (tertiles), mg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Description: information on median arsenic level in artesian well water of each village acquired from previous studies carried out in the early 1960s (Lai et al., 1994); some study subjects had moved from one village to another, and there were differences in arsenic concentrations between villages **Population-Level Exposure:** 0.7-0.93 mg/L range	Exp. Level / n / HR / (CI) <0.05 / 7 / 1 / n/a 0.05-0.71 / 20 / 0.81 / 0.33, 1.97 ≥ 0.71 / 30 / 1.04 / 0.43, 2.48 Stat Method: Cox proportional hazard model
	Exposure Surrogate: urine **Exposure Description:** urine samples of 1078 subjects collected at time of recruitment; all arsenic assays performed within 6 months of sample collection **Population-Level Exposure:** not available	**Outcome: lung cancer** ***percent DMA in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) ≥ 85.8 / 14 / 1 / n/a 76.13-85.8 / 17 / 0.97 / 0.47, 1.98 <76.13 / 15 / 0.81 / 0.38, 1.71 Stat Method: Cox proportional hazard model ***percent inorganic arsenic in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) <4.22 / 11 / 1 / n/a 4.22-7.86 / 20 / 1.98 / 0.94, 4.17 ≥ 7.86 / 15 / 1.43 / 0.66, 3.14 Stat Method: Cox proportional hazard model ***percent MMA in total urinary arsenic concentration (tertiles), %*** Exp. Level / n / adjOR / (CI) <8.34 / 14 / 1 / n/a 8.34-15.31 / 15 / 1.04 / 0.5, 2.15 ≥ 15.31 / 17 / 0.85 / 0.41, 1.76 Stat Method: Cox proportional hazard model
Dauphiné et al. (2011) **Study Type:** cohort (retrospective) **Location:** Chile (Antofagasta and Arica)	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration calculated from municipal drinking water records and each individual's residential history **Population-Level Exposure:**	**Outcome: any respiratory symptom** ***peak water arsenic concentration before age 10 (0-250 reference), µg/L*** Exp. Level / n / adjOR / (CI) 0-250 / NR / 1 / n/a >800 / NR / 2.63 / 0.78, 8.92 Stat Method: multivariate logistic regression **Outcome: FEV-1 residual (ml)**

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Population: adult nursing school employees living in village with history of higher than average arsenic in drinking water n exposed: 32 n reference: 65 n total: 97	0-800 µg/L	***peak water arsenic concentration before age 10 (<50 reference), µg/L*** Exp. Level / n / adjBeta / (CI) <50 / NR / 0 / n/a 50-250 / NR / -152 / n/a >800 / NR / -335 / n/a Stat Method: multivariate linear regression **Outcome: FVC residual (ml)** ***peak water arsenic concentration before age 10 (<50 reference), µg/L*** Exp. Level / n / adjBeta / (CI) <50 / NR / 0 / n/a 50-250 / NR / -52 / n/a >800 / NR / -429 / n/a Stat Method: multivariate linear regression **Outcome: percent predicted FEV-1** ***peak water arsenic concentration before age 10 (<50 reference), µg/L*** Exp. Level / n / adjBeta / (CI) <50 / NR / 0 / n/a 50-250 / NR / -4.6 / n/a >800 / NR / -11.5 / n/a Stat Method: multivariate linear regression **Outcome: percent predicted FVC** ***peak water arsenic concentration before age 10 (<50 reference), µg/L*** Exp. Level / n / adjBeta / (CI) <50 / NR / 0 / n/a 50-250 / NR / -2.7 / n/a >800 / NR / -12.2 / n/a Stat Method: multivariate linear regression
Dauphiné et al. (2013) **Study Type:** case-control **Location:** United States (CA; NV) **Population:** residents	**Exposure Surrogate:** drinking water **Exposure Description:** over 7,000 arsenic measurements for community-supplied drinking water and thousands of private domestic wells within study area provided by Nevada State Health Division and California Department of Health Services; participants asked over phone how many glasses of water and water-	**Outcome: lung cancer** ***highest 5-year average arsenic concentration: 40-year lag, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 10 / 169 / 1 / n/a 11-84 / 15 / 0.84 / 0.40, 1.79 ≥ 85 / 12 / 1.39 / 0.55, 3.53 Stat Method: unconditional logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
with lung cancer n cases: 196 n control: 359	based beverages and foods typically consumed 1 year prior to interview or diagnosis, as well as 20 and 40 years before **Population-Level Exposure:** 36 µg/L mean, 0-1460 µg/L range	
Farzan et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (NH) **Population:** 4 month old infants born to women 18-45 years old n total: 214	**Exposure Surrogate:** urine **Exposure Description:** mothers provided spot urine sample upon enrollment (24-28 weeks gestation); samples that registered below the detection limit assigned a value equal to the detection limit divided by the square root of two; total urinary As calculated as the sum of inorganic As (As[III] and As[V]) and metabolic products MMA(V) and DMA(V), excluding arsenobetaine **Population-Level Exposure:** 6 µg/L mean 7.5SD	**Outcome: acute respiratory symptoms, conditions, illnesses** ***maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L*** Exp. Level — n — RR — (CI) continuous: at least one infection — 74 — 1.1 — 0.8, 1.6 continuous: infection lasting 2 or more days — 57 — 1.3 — 0.9, 1.9 continuous: infection with a physician visit — 27 — 1.3 — 0.8, 2.0 continuous: infection treated with prescription medication — 5 — 4 — 1.0, 15.9 Stat Method: logistic regression **Outcome: any lower respiratory tract infection** ***maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L*** Exp. Level — n — RR — (CI) continuous: at least one infection — 9 — 1.4 — 0.7, 3.1 continuous: infection lasting 2 or more days — 9 — 1.4 — 0.7, 3.1 continuous: infection with a — 9 — 1.4 — 0.7, 3.1

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		physician visit continuous: infection treated with prescription medication 7 3.3 1.2, 9.0 Stat Method: logistic regression
		Outcome: any respiratory tract infection
		maternal urinary As (ln transformed; categorized by two infection descriptions), µg/L Exp. Level n RR (CI) with a physician visit NR 1.5 1.0, 2.1 treated with prescription medication NR 1.6 1.1, 2.4 Stat Method: Poisson model
		Outcome: any upper respiratory tract infection
		maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L Exp. Level n RR (CI) continuous: at least one infection 133 1.1 0.8, 1.6 continuous: infection lasting 2 or more days 111 1.2 0.9, 1.7 continuous: infection with a physician visit 53 1.1 0.8, 1.6 continuous: infection treated with prescription medication 28 1.6 1.0, 2.5 Stat Method: logistic regression
		Outcome: cold, runny, or stuffed nose

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L Exp. Level / n / RR / (CI) continuous: at least one infection / 126 / 1 / 0.8, 1.4 continuous: infection lasting 2 or more days / 103 / 1.1 / 0.8, 1.5 continuous: infection with a physician visit / 39 / 1 / 0.7, 1.4 continuous: infection treated with prescription medication / 9 / 2.3 / 1.0, 5.2 Stat Method: logistic regression
		Outcome: ear infection (otitis media)
		maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L Exp. Level / n / RR / (CI) continuous: at least one infection / 8 / 1.1 / 0.5, 2.6 continuous: infection lasting 2 or more days / 8 / 1.1 / 0.5, 2.6 continuous: infection with a physician visit / 7 / 1.6 / 0.7, 3.8 continuous: infection treated with prescription medication / 7 / 1.6 / 0.7, 3.8 Stat Method: logistic regression
		Outcome: eye infection (conjuctivitis)

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		maternal urinary As (ln transformed; categorized by 4 infection descriptions), µg/L Exp. Level / n / RR / (CI) continuous: at least one infection / 17 / 1.4 / 0.8, 2.4 continuous: infection lasting 2 or more days / 14 / 1.4 / 0.6, 2.6 continuous: infection with a physician visit / 14 / 1.6 / 0.9, 2.9 continuous: infection treated with prescription medication / 14 / 1.2 / 0.7, 2.1 Stat Method: logistic regression
Ferreccio et al. (2000) **Study Type:** case-control **Location:** Chile (Regions I, II, III in northern Chile) **Population:** public hospital adult patients in areas with low to high drinking water arsenic exposure n cases: 151 n control: 419	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentrations measured by water companies (1950-1994) or estimated based on 1950s concentrations (1930-1957); individual exposure calculated using self-reported residential history and yearly average water arsenic concentration for each county of residence; lifetime average exposure based on 1930-1994 concentrations; peak average exposure based on 1958-1970 concentrations **Population-Level Exposure:** 0-400 µg/L range	**Outcome: lung cancer** ***lifetime water arsenic concentration (1930-1994), µg/L*** Exp. Level / n / adjOR / (CI) 0-10 / 9 / 1 / n/a 10-29 / 5 / 1.6 / 0.5, 5.3 30-49 / 8 / 3.9 / 1.2, 12.3 50-199 / 50 / 5.2 / 2.3, 11.7 200-400 / 79 / 8.9 / 4.0, 19.6 Stat Method: unconditional regression analysis ***peak years average water arsenic concentration (1958-1970), µg/L*** Exp. Level / n / adjOR / (CI) 0-10 / 11 / 1 / n/a 10-29 / 3 / 0.3 / 0.1, 1.2 30-59 / 4 / 1.8 / 0.5, 6.9 60-89 / 22 / 4.1 / 1.8, 9.6 90-199 / 13 / 2.7 / 1.0, 7.1 200-399 / 23 / 4.7 / 2.0, 11.0 400-699 / 11 / 5.7 / 1.9, 16.9 700-999 / 64 / 7.1 / 3.4, 14.8 Stat Method: unconditional regression

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		analysis
Ferreccio et al. (2013b) **Study Type:** case-control **Location:** Chile (Regions I and II, Northern Chile) **Population:** residents with bladder or lung cancer in area formerly having arsenic-contaminated drinking water n cases: 538 n control: 640	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime arsenic exposure estimated by linking subject's residence with water arsenic concentration **Population-Level Exposure:** 0-800 µg/L range	**Outcome: lung cancer** ***water arsenic concentration - never smoker, µg/L*** Exp. Level / n / adjOR / (CI) <11 / 16 / 1 / n/a >355 / 18 / 2 / 0.8, 5.0 Stat Method: Unconditional logistic regression ***water arsenic concentration - smoked >10 cigarettes/day, µg/L*** Exp. Level / n / adjOR / (CI) <11 never smoker / NR / 1 / n/a <11 / 28 / 3.8 / 1.7, 8.5 >355 / 46 / 16 / 6.5, 40 Stat Method: Unconditional logistic regression
García-Esquinas et al. (2013) **Study Type:** cohort (prospective) **Location:** United States (AZ; ND; OK; SD) **Population:** Strong Heart Study participants n total: 3,935	**Exposure Surrogate:** urine **Exposure Description:** individual urine samples collected and analyzed for arsenic speciation **Population-Level Exposure:** 9.7 µg/g-creatinine median, 5.8-15.6 µg/g-creatinine 25th percentile	**Outcome: lung cancer** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 80th vs. 20th percentiles / 78 / 1.56 / 1.02, 2.39 Stat Method: Cox proportional hazard models
Ghosh et al. (2007b) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** West Bengal residents	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic content in drinking water measured from 100 ml samples provided by study participants; instrument calibrated and readings taken in duplicate for each sample **Population-Level Exposure:** 0-1188 µg/L range	**Outcome: respiratory illness** ***arsenic exposure/skin lesion status, µg/L*** Exp. Level / n / adjOR / (CI) unexposed / 13 / 1 / n/a exposed, no skin lesions / 32 / 3.21 / 1.65, 6.26 exposed, skin lesions / 118 / 13.54 / 7.45, 24.62 Stat Method: Logistic regression analysis

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
exposed to arsenic in drinking water with and without skin lesions and similar unexposed residents n cases: 725 n control: 389		
Guo et al. (2007) **Study Type:** cross-sectional **Location:** Mongolia region not available **Population:** residents of villages in the Hetao Plain, Inner Mongolia n cases: 680 n control: 189	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic samples were taken from 94 water sources, including wells; detection limit not specified, but authors note reliability of the method at <10 µg/L; arsenic exposure determined by location of village **Population-Level Exposure:** 50-1860 µg/L range	**Outcome: chronic bronchitis** ***water arsenic concentration, µg/L*** arsenic not significantly associated with bronchitis
Heck et al. (2009) **Study Type:** case-control **Location:** United States (NH; VT) **Population:** New England Lung Cancer Study, adult lung cancer cases n cases: 223 n control: 238	**Exposure Surrogate:** toenails **Exposure Description:** toenail arsenic concentration measured from individual cleaned clippings obtained during interview; results below LOD assigned 0.0015 µg/g **Population-Level Exposure:** 0.05-0.1137 µg/g range	**Outcome: all lung cancers** ***toenail arsenic concentration (quartiles), µg/g*** Exp. Level / n / adjOR / (CI) <0.05 / 65 / 1 / n/a 0.05-<0.0768 / 58 / 1.34 / 0.71, 2.53 0.0768-<0.1137 / 58 / 1.1 / 0.55, 2.20 ≥ 0.1137 / 57 / 0.89 / 0.46, 1.75 Stat Method: Unconditional logistic regression **Outcome: lung cancer cell types previously associated with arsenic (small cell and squamous cells)** ***toenail arsenic concentration (quartiles), µg/g*** Exp. Level / n / adjOR / (CI) <0.05 / 65 / 1 / n/a 0.05-<0.0768 / 58 / 2.99 / 1.12, 7.99 0.0768-<0.1137 / 58 / 1.86 / 0.62, 5.58 ≥ 0.1137 / 57 / 2.75 / 1.00, 7.57 Stat Method: Unconditional logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Hsu et al. (2013a) **Study Type:** cohort (prospective) **Location:** Taiwan (Peimen, Hsuechia, Putai, Ichu townships) **Population:** 3 separate subcohorts of residents of an arseniasis-endemic area n exposed: 1075 n reference: 535 n total: 2447	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime cumulative arsenic exposure estimated using median arsenic concentration in village well where study subject lived and duration of exposure; arsenic concentrations in wells obtained from 2 investigations examining more than 38,565 wells across Taiwan; lifetime cumulative arsenic exposure (CAE) estimated using median arsenic concentration in village well where study subject lived and duration of exposure **Population-Level Exposure:** 1-20 mg/L - yr range	**Outcome: lung cancer** ***cumulative arsenic exposure, mg/L - yr*** Exp. Level / n / HR / (CI) <1.0 / NR / 1 / n/a 1.0-19.9 / NR / 0.8 / 0.46, 1.4 ≥ 20 / NR / 0.73 / 0.38, 1.42 missing / NR / 0.65 / 0.38, 1.12 Stat Method: Cox regression analysis with time-dependent covariates
Khlifi et al. (2014) **Study Type:** case-control **Location:** Tunisia (Sfax and South Tunisia) **Population:** hospital patients with laryngeal or nasopharyngeal cancer n cases: 145 n control: 351	**Exposure Surrogate:** blood **Exposure Description:** 3 mL venous blood samples collected from patients at diagnosis and analyzed for arsenic and cadmium **Population-Level Exposure:** 0.83 µg/L median, 0.13-42 µg/L range	**Outcome: laryngeal cancer (LC): differentiated epidermoid carcinoma** ***blood arsenic level - continuous, µg/L*** Exp. Level / n / adjOR / (CI) blood arsenic level / NR / 1.14 / 1.05, 1.42 Stat Method: conditional logistic regression ***blood arsenic levels, µg/L*** Exp. Level / n / adjOR / (CI) Low (≤ 2.32 µg/L) / 49 / 1 / n/a High (>2.32 µg/L) / 48 / 2.63 / 1.50, 4.34 Stat Method: logistic regression analysis **Outcome: laryngeal cancer + nasopharyngeal cancer** ***blood arsenic level - continuous, µg/L*** Exp. Level / n / adjOR / (CI) blood arsenic level / NR / 1.16 / 1.08, 1.26 Stat Method: conditional logistic regression ***blood arsenic levels, µg/L*** Exp. Level / n / adjOR / (CI) Low (≤ 2.32 µg/L) / 76 / 1 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		High (>2.32 µg/L) 69 2.41 1.56, 3.71 Stat Method: logistic regression analysis
		Outcome: nasopharyngeal cancer (NPC): undifferentiated carcinoma
		blood arsenic level - continuous, µg/L Exp. Level / n / adjOR / (CI) blood arsenic level NR 1.16 1.06, 1.28 Stat Method: conditional logistic regression
		blood arsenic levels, µg/L Exp. Level / n / adjOR / (CI) Low (≤ 2.32 µg/L) 27 1 n/a High (>2.32 µg/L) 21 2.18 1.15, 4.12 Stat Method: logistic regression analysis
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** male and female members of Latter-day Saints church wards n exposed: 2203 n total: 2203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: bronchitis, emphysema, asthma**
		cumulative arsenic exposure, ppb-years SMR for bronchitis, emphysema, and asthma unchanged from expected in males and females
		Outcome: nonmalignant respiratory disease
		cumulative arsenic exposure, ppb-years SMR for nonmalignant respiratory disease unchanged from expected in females; SMR significantly decreased in medium exposure males only
		Outcome: respiratory system cancer
		cumulative arsenic exposure (females), ppb-years Exp. Level / n / SMR / (CI) <1000 NR 0.44 n/a 1000-4999 NR 0.66 n/a ≥ 5000 NR 0.22 n/a Stat Method: standardized mortality ratios
		cumulative arsenic exposure (males), ppb-years Exp. Level / n / SMR / (CI) <1000 NR 0.32 n/a 1000-4999 NR 0.96 n/a ≥ 5000 NR 0.44 n/a Stat Method: standardized mortality ratios

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Majumdar et al. (2009) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** residents of arsenic-affected villages n cases: 3825 n control: 3451	**Exposure Surrogate:** drinking water **Exposure Description:** for each participant, water samples from private or public tube wells analyzed for arsenic; exposure categories developed based on arsenic levels **Population-Level Exposure:** 50-500 µg/L range	**Outcome: chronic lung disease** ***arsenic concentration in drinking water (females), µg/L*** Exp. Level / n / prevOR / (CI) <50 / NR / 1 / n/a ≥ 500 / NR / 1.76 / 1.1, 2.6 Stat Method: prevalence odds ratio calculated for each outcome comparing highest and lowest exposure levels ***arsenic concentration in drinking water (males), µg/L*** Exp. Level / n / prevOR / (CI) <50 / NR / 1 / n/a ≥ 500 / NR / 0.93 / 0.65, 1.3 Stat Method: prevalence odds ratio calculated for each outcome comparing highest and lowest exposure levels
Nafees et al. (2011) **Study Type:** cross-sectional **Location:** Pakistan (Mehtani and Mian Jan Muhammad Abbassi villages) **Population:** adults and children living in villages with high proportion of contaminated drinking water sources n cases: 100 n control: 100	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water concentration calculated from samples tested at field site using portable kits; source more frequently used for drinking water tested when multiple sources used; subjects grouped for analysis as exposed (≥ 100 µg/L; ≥ 250 µg/L) **Population-Level Exposure:** 10-250 µg/L range	**Outcome: FEV1 (mL)** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) ≥ 100 / NR / -154.3 / -324.7, 16.0 Stat Method: Multivariate linear regression ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) ≥ 250 / NR / -226.4 / -430.4, -22.4 Stat Method: Multivariate linear regression **Outcome: FEV1/FVC** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) ≥ 100 / NR / 2 / -25.3, 29.4 Stat Method: Multivariate linear regression ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) ≥ 250 / NR / 9.9 / -21.8, 41.6 Stat Method: Multivariate linear regression **Outcome: FVC (mL)** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjBeta / (CI) ≥ 100 / NR / -221.9 / -419.5, -24.3

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: Multivariate linear regression
		drinking water arsenic concentration, µg/L Exp. Level / n / adjBeta / (CI) ≥ 250 / NR / -354.8 / -583.6, -126.0 Stat Method: Multivariate linear regression
Parvez et al. (2013) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** subset of Health Effects of Arsenic Longitudinal Study (HEALS) participants with respiratory symptoms n total: 950	**Exposure Surrogate:** drinking water **Exposure Description:** field sample collection and laboratory analyses of water samples; arsenic concentration noted to be relatively stable and not to change over time under normal conditions; information on the status of well and water consumption behavior and pattern from the study participants collected **Population-Level Exposure:** 19-97 µg/L range	**Outcome: lung function: forced expiratory volume (FEV1)**
		well water arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) <19 / NR / 0 / n/a >19-97 / NR / -33.1 / -114.6, 48.4 >97 / NR / -80.6 / -181.4, -17.5 Stat Method: multivariate logistic regression
		well water arsenic concentration - per one SD (118.1 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -46.5 / -83.0, -10.0 Stat Method: multivariate logistic regression
		Outcome: lung function: forced vital capacity (FVC)
		well water arsenic concentration (tertiles), µg/L Exp. Level / n / adjBeta / (CI) <19 / NR / 0 / n/a >19-97 / NR / -13.2 / -97.3, 71.0 >97 / NR / -97.3 / -181.8, -12.7 Stat Method: multivariate logistic regression
		well water arsenic concentration - per one SD (118.1 µg/L), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -53.1 / -90.7, -15.4 Stat Method: multivariate logistic regression
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic measured at baseline and biannually in spot urine samples **Population-Level Exposure:** 125-285 µg/g-creatinine	**Outcome: lung function: forced expiratory volume (FEV1)**
		urinary arsenic concentration (tertiles), µg/g-creatinine Exp. Level / n / adjBeta / (CI) <125 / NR / 0 / n/a >125-285 / NR / -67 / -148.3, 14.1 >285 / NR / -90.5 / -173.6, -7.4 Stat Method: multivariate logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		urinary arsenic concentration - per one SD (277.2 µg/g-creatinine), µg/g-creatinine Exp. Level / n / adjBeta / (CI) continuous / NR / -48.3 / -82.5, -14.1 Stat Method: multivariate logistic regression **Outcome: lung function: forced vital capacity (FVC)** ***urinary arsenic concentration (tertiles), µg/g-creatinine*** Exp. Level / n / adjBeta / (CI) <125 / NR / 0 / n/a >125-285 / NR / -36.4 / -120.4, 47.0 >285 / NR / -81 / -166.7, 4.8 Stat Method: multivariate logistic regression ***urinary arsenic concentration - per one SD (277.2 µg/g-creatinine), µg/g-creatinine*** Exp. Level / n / adjBeta / (CI) continuous / NR / -55.2 / -90.5, -19.9 Stat Method: multivariate logistic regression
Parvez et al. (2010) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study, adults participants who underwent first two follow-up visits n total: 10833	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentration based on water samples collected from wells from which study participants drank regularly; results <LOD analyzed using second method **Population-Level Exposure:** 7-178 µg/L range	**Outcome: blood in sputum** ***drinking water arsenic concentration (quintiles), µg/L*** Exp. Level / n / HR / (CI) ≤ 7 / NR / 1 / n/a 7-40 / NR / 1.15 / 0.75, 1.76 7 - 40 40-90 / NR / 1.09 / 1.69, 1.70 90-178 / NR / 1.66 / 1.10, 2.51 >178 / NR / 1.51 / 0.98, 2.32 Stat Method: Cox proportional hazard models **Outcome: breathing problem** ***drinking water arsenic concentration (quintiles), µg/L*** Exp. Level / n / HR / (CI) ≤ 7 / NR / 1 / n/a 7-40 / NR / 1.44 / 1.20, 1.74 7 - 40 40-90 / NR / 1.52 / 1.25, 1.84 90-178 / NR / 1.42 / 1.16, 1.73 >178 / NR / 1.41 / 1.56, 1.72 Stat Method: Cox proportional hazard models

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: chronic cough ***drinking water arsenic concentration (quintiles), µg/L*** Exp. Level / n / HR / (CI) ≤ 7 / NR / 1 / n/a 7-40 / NR / 1.19 / 0.95, 1.5 7 - 40 40-90 / NR / 1.4 / 1.11, 1.75 90-178 / NR / 1.57 / 1.25, 1.97 >178 / NR / 1.6 / 1.27, 2.01 Stat Method: Cox proportional hazard models
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic concentration measured from spot samples collected at each visit **Population-Level Exposure:** 90-406 µg/g-creatinine range	**Outcome: blood in sputum** ***urinary arsenic concentration (quintiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) ≤ 90 / NR / 1 / n/a 90-160 / NR / 1.16 / 0.77, 1.74 160-246 / NR / 1.05 / 0.69, 1.60 246-406 / NR / 1.03 / 0.67, 1.58 >406 / NR / 1.33 / 0.89, 1.99 Stat Method: Cox proportional hazard models
		Outcome: breathing problem ***urinary arsenic concentration (quintiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) ≤ 90 / NR / 1 / n/a 90-160 / NR / 1.14 / 0.95, 1.38 160-246 / NR / 1.16 / 0.96, 1.40 246-406 / NR / 1.28 / 1.06, 1.54 >406 / NR / 1.27 / 1.05, 1.53 Stat Method: Cox proportional hazard models
		Outcome: chronic cough ***urinary arsenic concentration (quintiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) ≤ 90 / NR / 1 / n/a 90-160 / NR / 0.98 / 0.78, 1.23 160-246 / NR / 1.14 / 0.91, 1.42 246-406 / NR / 1.52 / 1.23, 1.88 >406 / NR / 1.51 / 1.21, 1.87 Stat Method: Cox proportional hazard models

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Paul et al. (2013) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** male and female adult residents with skin lesions from 3 villages with high arsenic concentrations n cases: 189 n control: 171	**Exposure Surrogate:** drinking water **Exposure Description:** samples collected directly from study participants during 2005-2006 and 2010-2011 study periods **Population-Level Exposure:** mean concentration in drinking water ranged from 3.7 (unexposed) to 190.1 (exposed) in both analyses	**Outcome: respiratory problems/respiratory disorders** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / OR / (CI) unexposed (2005-2006 analysis) / NR / 1 / n/a unexposed (2010-2011 analysis) / NR / 1 / n/a exposed (2005-2006 analysis) / NR / 6.07 / 2.47, 14.95 exposed (2010-2011 analysis) / NR / 11.45 / 5.04, 25.94 Stat Method: OR with 95% CI; 2005 - 2006 data compared to 2010 - 2011 data using Chi-Square test.
Rahman et al. (2011) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** MINIMat Study, mother-infant pairs n total: 1552	**Exposure Surrogate:** maternal urine **Exposure Description:** maternal urinary arsenic concentration measured from urine samples collected at GW 8 and 30; arsenic exposure calculated as sum of inorganic arsenic and its methylated metabolites (MMA and DMA) and the average of exposure at GW 8 and 30; samples <LOD reanalyzed using larger volume; groups are quintiles **Population-Level Exposure:** 159 µg/L mean 163SD	**Outcome: LRTI** ***maternal urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjRR / (CI) <39 / NR / 1 / n/a 39-64 / NR / 1.28 / 1.02, 1.61 65-132 / NR / 1.33 / 1.07, 1.67 133-261 / NR / 1.57 / 1.27, 1.96 ≥ 261 / NR / 1.69 / 1.36, 2.09 Stat Method: Poisson regression **Outcome: severe LRTI** ***maternal urinary arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjRR / (CI) <39 / NR / 1 / n/a 39-64 / NR / 1.33 / 1.03, 1.71 65-132 / NR / 1.31 / 1.02, 1.69 133-261 / NR / 1.54 / 1.21, 1.97 ≥ 261 / NR / 1.54 / 1.21, 1.97 Stat Method: Poisson regression
Raqib et al. (2009)	**Exposure Surrogate:** urine	**Outcome: acute respiratory infection at 6-12 months** ***maternal urinary arsenic at gestation week 30,***

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** women and infants enrolled in MINIMat study of nutritional impact on fetal and infant development n total: 140	**Exposure Description:** maternal urine samples taken at gestation week 8 or 30 analyzed for inorganic arsenic and metabolites; samples adjusted for specific gravity **Population-Level Exposure:** 145.8 µg/L mean 186.8SD	***µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 0.004 / 0.001, 0.006 Stat Method: multiple linear regression
Sawada et al. (2013) **Study Type:** cohort (prospective) **Location:** Japan (Iwate, Akita, Nagano, Okinawa, Tokyo, Ibaraki, Niigata, Kochi, Nagasaki, Osaka) **Population:** adults in Japan Public Health Center (JPHC) Prospective Study cohort n total: 90378	**Exposure Surrogate:** diet **Exposure Description:** detailed questionnaire on food intake/frequency; average arsenic concentrations in food items obtained from the literature; arsenic intake calculated by multiplying average arsenic concentration in each item by quantity consumed **Population-Level Exposure:** 170 µg/day mean, 88.3-253.2 µg/day range	**Outcome: lung cancer** ***inorganic arsenic intake (tertiles; females; never smoker), µg/day*** Exp. Level / n / HR / (CI) lowest tertile / 58 / 1 / n/a middle tertile / 74 / 1.31 / 0.92, 1.86 highest tertile / 92 / 1.57 / 1.12, 2.20 Stat Method: Cox's proportional hazards model ***inorganic arsenic intake (tertiles; males; current smoker), µg/day*** Exp. Level / n / HR / (CI) lowest tertile / 115 / 1 / n/a middle tertile / 137 / 1.2 / 0.93, 1.55 highest tertile / 166 / 1.38 / 1.07, 1.77 Stat Method: Cox's proportional hazards model ***inorganic arsenic intake (tertiles; males; ever smoker), µg/day*** Exp. Level / n / HR / (CI) lowest tertile / 149 / 1 / n/a middle tertile / 158 / 1.07 / 0.85, 1.34 highest tertile / 215 / 1.36 / 1.09, 1.7 Stat Method: Cox's proportional hazards model ***total arsenic intake (tertiles; males; current***

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		smoker), µg/day Exp. Level / n / HR / (CI) lowest tertile / 101 / 1 / n/a middle tertile / 153 / 1.41 / 1.09, 1.82 highest tertile / 164 / 1.37 / 1.06, 1.77 Stat Method: Cox's proportional hazards model
		total arsenic intake (tertiles; males; ever smoker), µg/day Exp. Level / n / HR / (CI) lowest tertile / 135 / 1 / n/a middle tertile / 180 / 1.24 / 0.99, 1.56 highest tertile / 207 / 1.29 / 1.03, 1.61 Stat Method: Cox's proportional hazards model
Smith et al. (2013) **Study Type:** cohort (prospective) **Location:** Bangladesh (Matlab) **Population:** children in rural area n exposed: 491 n reference: 159 n total: 650	**Exposure Surrogate:** drinking water **Exposure Description:** water samples were collected from all functioning tube wells used at home and at school; in utero exposure assessed during 9 months of pregnancy based on tube well concentrations with levels from the 2002-2003 survey used for any tube wells where samples could not be collected and residential histories starting 1 year prior to the childs birth to the current residence **Population-Level Exposure:** 436.8 µg/L mean	**Outcome: asthma** ***in utero arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) 10-199 / NR / 1.23 / 0.50, 3.02 200-399 / NR / 1.88 / 0.90, 3.92 400-599 / NR / 2.23 / 1.13, 4.49 ≥ 600 / NR / 2.38 / 1.17, 4.83 NR / NR / 1 / n/a Stat Method: multiple linear regression analysis **Outcome: coughing - no cold** ***in utero arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) 10-199 / NR / 2.37 / 0.92, 6.09 200-399 / NR / 1.62 / 0.64, 4.11 400-599 / NR / 1.78 / 0.74, 4.31 ≥ 600 / NR / 2.47 / 1.05, 5.79 NR / NR / 1 / n/a Stat Method: multiple linear regression analysis **Outcome: FEV1** ***in utero arsenic exposure (continuous), µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / -0.013 / -0.076, 0.049

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multiple linear regression analysis
		in utero arsenic exposure (tertiles), µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 0 / n/a 10-499 / NR / 16.4 / -25.5, 58.3 500+ / NR / -22.6 / -72.7, 27.6 Stat Method: multiple linear regression analysis
		Outcome: FVC
		in utero arsenic exposure (continuous), µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / -0.007 / -0.075, 0.061 Stat Method: multiple linear regression analysis
		in utero arsenic exposure (tertiles), µg/L Exp. Level / n / adjBeta / (CI) <10 / NR / 0 / n/a 10-499 / NR / 27 / -18.5, 72.5 500+ / NR / -17.2 / -71.6, 37.3 Stat Method: multiple linear regression analysis
		Outcome: shortness of breath - fast walking/climbing
		in utero arsenic exposure (quartiles), µg/L Exp. Level / n / adjOR / (CI) 10-199 / NR / 1.07 / 0.27, 4.28 200-399 / NR / 2.89 / 1.06, 7.91 400-599 / NR / 4.09 / 1.56, 10.7 ≥ 600 / NR / 3.2 / 1.18, 8.71 NR / NR / NR / n/a Stat Method: multiple linear regression analysis
		Outcome: shortness of breath - walking
		in utero arsenic exposure (quartiles), µg/L Exp. Level / n / adjOR / (CI) 10-199 / NR / 1.3 / 0.72, 7.58 200-399 / NR / 2.21 / 0.54, 9.12 400-599 / NR / 4.5 / 1.17, 17.3 ≥ 600 / NR / 3.37 / 0.88, 12.8

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		NR NR NR n/a Stat Method: multiple linear regression analysis **Outcome: wheezing (ever)** ***in utero arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) 10-199 NR 1.98 1.03, 3.80 200-399 NR 1.51 0.83, 2.74 400-599 NR 3.17 1.78, 5.64 ≥ 600 NR 2.12 1.19, 3.76 NR NR 1 n/a Stat Method: multiple linear regression analysis **Outcome: wheezing - no cold** ***in utero arsenic exposure (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) 10-199 NR 5.01 0.78, 32.0 200-399 NR 1.57 0.20, 12.1 400-599 NR 8.65 1.64, 45.7 ≥ 600 NR 8.21 1.56, 43.1 NR NR NR n/a Stat Method: multiple linear regression analysis
Steinmaus et al. (2013) **Study Type:** case-control **Location:** Chile (Antofagasta) **Population:** residents with lung cancer or bladder cancer who were formerly exposed to high arsenic levels in drinking water n cases: 538 n control: 640	**Exposure Surrogate:** drinking water **Exposure Description:** drinking water arsenic concentrations for each city or town in the study area collected from government agencies, research studies, and water suppliers; subjects self-reported daily water intake **Population-Level Exposure:** 1578-12841 µg/L - yr range	**Outcome: lung cancer** ***cumulative arsenic concentration: all years (quartiles), µg/L - yr*** Exp. Level / n / adjOR / (CI) <1578 60 1 n/a 1578-4876 61 0.95 0.61, 1.50 4877-12841 89 1.89 1.19, 3.02 >12841 96 2.9 1.69, 4.97 Stat Method: Unconditional logistic regression ***cumulative arsenic concentration: before 1971 (quartiles), µg/L - yr*** Exp. Level / n / adjOR / (CI) <372 51 1 n/a 372-2464 64 1.29 0.82, 2.02 2465–10319 87 2.4 1.51, 3.81 >10319 100 4.82 2.79, 8.34 Stat Method: Unconditional logistic

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		regression
		cumulative arsenic intake: all years (quartiles), ug Exp. Level / n / adjOR / (CI) <2438 / 64 / 1 / n/a 2438-8214 / 58 / 0.84 / 0.54, 1.32 8215-19093 / 77 / 1.29 / 0.81, 2.06 >19093 / 107 / 3.25 / 2.00, 5.29 Stat Method: Unconditional logistic regression
		cumulative arsenic intake: before 1971 (quartiles), ug Exp. Level / n / adjOR / (CI) <576 / 53 / 1 / n/a 576–4429 / 63 / 1.21 / 0.77, 1.89 4430–14347 / 78 / 1.92 / 1.22, 3.03 >14347 / 108 / 4.86 / 2.92, 8.09 Stat Method: Unconditional logistic regression
		lifetime average arsenic concentration: all years (quartiles), µg/L Exp. Level / n / adjOR / (CI) <26 / 61 / 1 / n/a 26-79 / 61 / 0.98 / 0.62, 1.53 80-197 / 85 / 1.7 / 1.05, 2.75 >197 / 99 / 3.18 / 1.90, 5.30 Stat Method: Unconditional logistic regression
		lifetime average arsenic concentration: before 1971 (quartiles), µg/L Exp. Level / n / adjOR / (CI) <11 / 51 / 1 / n/a 11-90 / 66 / 1.27 / 0.81, 1.98 91-335 / 80 / 2 / 1.24, 3.24 >335 / 105 / 4.32 / 2.60, 7.17 Stat Method: Unconditional logistic regression
		lifetime daily average arsenic intake: all years (quartiles), µg/day Exp. Level / n / adjOR / (CI) >41 / 64 / 1 / n/a 41-136 / 56 / 0.87 / 0.55, 1.36

Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects		
Reference and Study Design	**Exposure Measures**	**Results**
		137-307 76 1.24 0.78, 1.98 >307 110 3.16 1.98, 5.03 Stat Method: Unconditional logistic regression
		lifetime daily average arsenic intake: before 1971 (quartiles), µg/day Exp. Level / n / adjOR / (CI) <21 53 1 n/a 21-159 64 1.19 0.76, 1.85 160-525 73 1.63 1.01, 2.65 >525 112 4.89 2.99, 7.99 Stat Method: Unconditional logistic regression
Tsuda et al. (1995) **Study Type:** cohort (retrospective) **Location:** Japan (Namiki-cho) **Population:** adults and children living near factory producing arsenic trisulfide n exposed: 189 n reference: 254 n total: 443	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in well water measured in 1959 (the end of the exposure period) in 34 wells; 20 area wells had no documented levels of arsenic so authors inferred that arsenic levels were undetectable or very low; concentration assigned based on residence in 1959 **Population-Level Exposure:** 0.05-1 ppm range	**Outcome: lung cancer** ***arsenic concentration in well water in 1959, ppm*** Exp. Level / n / SMR / (CI) <0.05 0 0 0, 2.43 0.05-0.99 1 2.33 0.12, 13.39 ≥ 1 8 15.69 7.38, 31.02 Stat Method: Cox proportional hazard

--: not reported; n: number of cases (when presented in Results column)

5.15.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Respiratory Effects

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5.16 Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Ahsan et al. (2000) **Study Type:** cross-sectional **Location:** Bangladesh (Sonargaon) **Population:** residents of three contiguous villages where well water had not been previously tested n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic measured in pitcher-water obtained directly from household (correlated with tube-well water samples); exposure stratified by quartiles **Population-Level Exposure:** 29-991 µg/L range	**Outcome: any skin lesions** ***arsenic in pitcher-water (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) ≤ 29 / NR / 1 / n/a >29-90 / NR / 0.9 / 0.3, 2.9 >90-278 / NR / 0.36 / 0.1, 1.2 >278-991 / NR / 1.67 / 0.6, 5.1 Stat Method: logistic regression models
	Exposure Surrogate: drinking water **Exposure Description:** cumulative arsenic index (CAI) calculated by multiplying arsenic concentration in pitcher water with estimated yearly water consumption and years of water source use (tube well concentration assumed to be constant); exposure stratified by quartiles **Population-Level Exposure:** 116.4-22147.1 mg range	**Outcome: any skin lesions** ***cumulative arsenic index (CAI) (quartiles), mg*** Exp. Level / n / adjOR / (CI) ≤ 116.4 / NR / 1 / n/a >116.4-474.9 / NR / 1.3 / 0.4, 4.4 >474.9-1279.9 / NR / 0.6 / 0.15, 2.2 >1279.9-22147.1 / NR / 2.3 / 0.7, 7.6 Stat Method: logistic regression models
	Exposure Surrogate: urine **Exposure Description:** individual urine samples, adjusted for creatinine content; exposure stratified by quartiles **Population-Level Exposure:** 122-1840 µg/L range	**Outcome: any skin lesions** ***total urinary arsenic concentration (quartiles), µg/L*** Exp. Level / n / adjOR / (CI) ≤ 122 / NR / 1 / n/a >122-244 / NR / 1 / 0.3, 3.6 >244-471 / NR / 2.1 / 0.6, 7.4 >471-1840 / NR / 3.6 / 1.2, 12.1 Stat Method: logistic regression models
	Exposure Surrogate: urine	**Outcome: any skin lesions** ***creatinine adjusted urinary arsenic concentration (quartiles), µg/g-creatinine***

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Description: individual urine samples; exposure stratified by quartiles **Population-Level Exposure:** 242-5727 µg/g-creatinine range	Exp. Level / n / adjOR / (CI) ≤ 242 / NR / 1 / n/a >242-440 / NR / 0.83 / 0.2, 2.9 >440-766 / NR / 0.88 / 0.2, 3.1 >766-5727 / NR / 3.22 / 1.1, 10.1 Stat Method: logistic regression models
Ahsan et al. (2006) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) subcohort exposed to full dose range of arsenic n cases: 11438 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic index calculated using well water arsenic concentration times daily consumption volume times duration of well use **Population-Level Exposure:** 0.1-9609 mg range	**Outcome: skin lesions** ***cumulative arsenic index, mg*** Exp. Level / n / adjOR / (CI) 0.1-48.1 / 53 / 1 / n/a 48.2-226.4 / 90 / 1.83 / 1.25, 2.69 226.5-582.6 / 122 / 2.53 / 1.72, 3.71 582.7-1485.8 / 162 / 3.62 / 2.5, 5.23 1485.9-9609.0 / 268 / 5.49 / 3.82, 7.90 Stat Method: Prevalence odds ratios (PORs) for skin lesions analyzed using unconditional logistic regression modeling
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted arsenic concentration calculated using drinking duration (data from interview) and well arsenic concentrations (if two wells used concentrations averaged) **Population-Level Exposure:** 0.1-864 µg/L range	**Outcome: skin lesions** ***time-weighted water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) 0.1-8.0 / 57 / 1 / n/a 8.1-40.0 / 90 / 1.91 / 1.26, 2.89 40.1-91.0 / 144 / 3.03 / 2.05, 4.50 91.1-175.0 / 162 / 3.71 / 2.53, 5.44 175.1-864.0 / 242 / 5.39 / 3.69, 7.86 Stat Method: Prevalence odds ratios (PORs) for skin lesions analyzed using unconditional logistic regression modeling
	Exposure Surrogate: urine **Exposure Description:** total urinary arsenic adjusted for creatinine concentration **Population-Level Exposure:** 6.6-4306 µg/g-creatinine range	**Outcome: skin lesions** ***urinary creatinine-adjusted arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) 6.6-90.1 / 60 / 1 / n/a 90.2-158.4 / 99 / 1.75 / 1.23, 2.48 158.5-243.4 / 129 / 2.33 / 1.67, 3.26 243.5-396.5 / 153 / 3.08 / 2.19, 4.35 396.6-4306.0 / 239 / 5.29 / 3.78, 7.41 unavailable / 15 / NR / n/a Stat Method: Prevalence odds ratios (PORs) for skin lesions analyzed using unconditional logistic regression modeling

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Argos et al. (2011) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) participants without skin lesions at baseline n exposed: 866 n reference: 9316 n total: 10182	**Exposure Surrogate:** drinking water **Exposure Description:** daily arsenic intake calculated by multiplying well water arsenic concentration of primary well (and secondary well if applicable) by daily consumption (self-reported) **Population-Level Exposure:** 0.4-472.1 µg/day range	**Outcome: incident skin lesions** ***daily arsenic intake, µg/day*** Exp. Level / n / HR / (CI) 0.4-19.4 / NR / 1 / n/a 19.5-100.8 / NR / 1.23 / 0.96, 1.58 100.9-233.1 / NR / 1.57 / 1.24, 1.99 233.2-472.0 / NR / 1.82 / 1.45, 2.30 ≥ 472.1 / NR / 2.92 / 2.34, 3.65 Stat Method: Multivariate model
	Exposure Surrogate: drinking water **Exposure Description:** well water samples in study area collected; samples below LOD reanalyzed; participants identified primary well of use at baseline **Population-Level Exposure:** 0.1-200.1 µg/L range	**Outcome: incident skin lesions** ***well water arsenic concentration, µg/L*** Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.17 / 0.92, 1.49 50.1-100 / NR / 1.69 / 1.33, 2.14 100.1-200 / NR / 1.97 / 1.58, 2.46 ≥ 200.1 / NR / 2.98 / 2.40, 3.71 Stat Method: Multivariate model
	Exposure Surrogate: urine **Exposure Description:** individual urinary total arsenic concentration measured and adjusted for creatinine **Population-Level Exposure:** 7-393 µg/g-creatinine range	**Outcome: incident skin lesions** ***creatinine adjusted urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / HR / (CI) 7-88 / NR / 1 / n/a 89-155 / NR / 0.9 / 0.71, 1.15 156-240 / NR / 1.34 / 1.07, 1.68 241-392 / NR / 1.62 / 1.29, 2.02 ≥ 393 / NR / 2.39 / 1.92, 2.97 Stat Method: Multivariate model
Baastrup et al. (2008) **Study Type:** cohort (prospective) **Location:** Denmark (Copenhagen and Aarhus) **Population:** Danish Cancer Registry population (adults)	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure and time-weighted average arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:**	**Outcome: melanoma skin cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 0.97 / 0.92, 1.03 Stat Method: Cox regression **Outcome: nonmelanoma skin cancer** ***cumulative arsenic exposure, mg*** Exp. Level / n / IRR / (CI) continuous / NR / 0.95 / 0.92, 0.97 Stat Method: Cox regression

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
n exposed: 56,378 n total: 57053	not available	
	Exposure Surrogate: drinking water **Exposure Description:** time-weighted and cumulative arsenic concentrations calculated for individuals based on residential address and history from Central Population Registry combined with measurement data from nearest water utility as recorded by Geological Survey of Denmark and Greenland (1987-2004) **Population-Level Exposure:** 0.7 µg/L median	**Outcome: melanoma skin cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 0.89 / 0.73, 1.07 Stat Method: Cox regression **Outcome: nonmelanoma skin cancer** ***time-weighted average arsenic exposure, µg/L*** Exp. Level / n / IRR / (CI) continuous / NR / 0.88 / 0.81, 0.94 Stat Method: Cox regression
Barati et al. (2010) **Study Type:** cross-sectional **Location:** Iran (Qorveh and Bijar cities, Kurdistan Province) **Population:** Western Iran residents with prevalence of multi-chronic arsenical poisoning as indicated by skin lesions, gangrene toes and fingers n cases: 587 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations measured in 530 village drinking water sources in the region; individual exposures estimated using village arsenic concentration **Population-Level Exposure:** 42-1500 µg/L range	**Outcome: depigmentation** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <50 / 1 / 1 / n/a 51-200 / 48 / 9.19 / 1.18, 71.01 201-500 / 42 / 10.34 / 1.33, 80.62 >500 / 11 / 9.29 / 1.09, 78.49 Stat Method: Mantel-Haenzel odds ratio **Outcome: gangrene** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <50 / 0 / NR / n/a 51-200 / 0 / NR / n/a 201-500 / 2 / 0.49 / 0.04, 5.79 >500 / 3 / 2.31 / 0.22, 24.31 Stat Method: Mantel-Haenzel odds ratio **Outcome: hyperpigmentation** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <50 / 1 / 1 / n/a 51-200 / 54 / 10.31 / 1.33, 79.72 201-500 / 39 / 9.61 / 1.23, 74.99 >500 / 13 / 10.04 / 1.19, 84.54 Stat Method: Mantel-Haenzel odds ratio **Outcome: keratosis**

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		drinking water arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) <50 / 3 / 1 / n/a 51-200 / 75 / 3.85 / 1.10, 13.91 201-500 / 47 / 5 / 1.41, 17.73 >500 / 17 / 4.34 / 1.10, 17.42 Stat Method: Mantel-Haenzel odds ratio
		Outcome: Mee's line
		drinking water arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) <50 / 2 / 1 / n/a 51-200 / 82 / 7.83 / 1.75, 34.94 201-500 / 54 / 6.65 / 1.45, 30.05 >500 / 19 / 7.34 / 1.50, 35.94 Stat Method: Mantel-Haenzel odds ratio
		Outcome: Multi-chronic arsenical poisoning cases
		drinking water arsenic concentration, µg/L Exp. Level / n / adjOR / (CI) <50 / NR / 1 / n/a 51-200 / NR / 1.96 / 0.56, 6.85 201-500 / NR / 3.65 / 1.03, 12.93 >500 / NR / 5.93 / 1.51, 23.25 Stat Method: Chi-square test, Mantel-Haenzel odds ratio
Bhowmick et al. (2013) **Study Type:** case-control **Location:** India (West Bengal) **Population:** participants from cross-sectional study carried out in several villages n cases: 64 n control: 37	**Exposure Surrogate:** saliva **Exposure Description:** saliva samples collected at interview **Population-Level Exposure:** 7.84 µg/L mean 12.6SD	**Outcome: skin lesion severity score**
		salivary arsenic concentration, µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.09 / 0.05, 0.13 Stat Method: multiple regression
	Exposure Surrogate: urine **Exposure Description:** participants provided urine samples at interview **Population-Level Exposure:** 110 µg/L mean 154SD	**Outcome: skin lesion severity score**
		urinary arsenic concentration, µg/L Exp. Level / n / adjBeta / (CI) continuous / NR / 0.11 / 0.04, 0.17 Stat Method: multiple regression
Breton et al. (2006)	**Exposure Surrogate:** toenails	**Outcome: Skin lesions**

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Study Type: case-control **Location:** Bangladesh (Pabna district) **Population:** Dhaka Community Hospital Trust clinic recruits n cases: n/a n control: n/a	**Exposure Description:** arsenic concentration in toenail clippings collected from every toe of each participant; arsenic analyzed in five replicate analyses **Population-Level Exposure:** 3.7 µg/g median	***toenail arsenic concentration, µg/g*** Exp. Level / n / adjOR / (CI) continuous / NR / 1.79 / 1.52, 2.10 Stat Method: Conditional logistic regression spline model (main effects model)
Chen et al. (2003a) **Study Type:** case-control **Location:** Taiwan (Southwestern Taiwan) **Population:** hospital patients with skin cancer or fracture/cataract n cases: 76 n control: 224	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated based on average arsenic concentration of artesian well water from the village in which subjects lived **Population-Level Exposure:** 0-15 mg/L - yr range	**Outcome: Skin cancer** ***cumulative arsenic exposure, mg/L - yr*** Exp. Level / n / adjOR / (CI) 0-2 / NR / 1 / n/a >2-15 / NR / 1.87 / 0.79, 4.45 >15 / NR / 2.99 / 1.30, 6.87 Stat Method: Multivariate logistic regression
Fatmi et al. (2009) **Study Type:** cross-sectional **Location:** Pakistan (Khairpur district, Sindh province) **Population:** residents of three villages with different levels of exposure n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure calculated by arsenic level in water source (weighted with proportion drinking from each source) multiplied by average drinking volume water and tea per day multiplied by duration (years) of drinking from same source per body weight; water samples taken from current drinking water sources and past sources when available within same village **Population-Level Exposure:** 10-100 µg/L-years/kg range	**Outcome: arsenic skin lesions (arsenicosis)** ***cumulative arsenic exposure, µg/L-years/kg*** Exp. Level / n / Prev / (CI) <10 / NR / 5.7 / n/a 10-<50 / NR / 11.8 / n/a 50-<100 / NR / 56.5 / n/a ≥ 100 / NR / 38.5 / n/a Stat Method: estimated prevalence per 1,000 population accounting for complex survey design (multi-stagecluster sampling)

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Surrogate: urine **Exposure Description:** arsenic concentrations in urine spot samples collected from all individuals with signs of arsenic skin lesions (suspected cases) and from two individuals (one male one female) without any arsenic skin lesions from each village **Population-Level Exposure:** 10-100 µg/L range	**Outcome: arsenic skin lesions (arsenicosis)** ***urinary arsenic concentration, µg/L*** Exp. Level / n / Prev / (CI) <10 / NR / 36.6 / n/a 10-<50 / NR / 99.5 / n/a 50-<100 / NR / 123.6 / n/a ≥ 100 / NR / 186 / n/a Stat Method: estimated prevalence per 1,000 population accounting for complex survey design (multi-stagecluster sampling)
Fatmi et al. (2013) **Study Type:** cross-sectional **Location:** Pakistan (Gambat in Khairpur district, Sindh province) **Population:** residents near Indus River exposed to elevated arsenic levels n cases: 72 n control: 462	**Exposure Surrogate:** drinking water **Exposure Description:** : arsenic concentrations in drinking water based on screening of 707 water sources serving 610 households; results compared to UNICEF survey for consistency; high-risk water sources randomly verified for arsenic level; personal reporting of duration of drinking from source **Population-Level Exposure:** 50-400 ppb range	**Outcome: arsenicosis** ***drinking water arsenic concentration, ppb*** Exp. Level / n / PR / (CI) >50-99 / 2 / 4.5 / 2.74, 6.26 100-299 / 47 / 14.8 / 10.88, 18.72 300-399 / 10 / 11.7 / 13.85, 20.23 ≥ 400 / 13 / 12.8 / 9.24, 14.76 Stat Method: Prevalence
Gilbert-Diamond et al. (2013) **Study Type:** case-control **Location:** United States (NH) **Population:** residents with invasive squamous cell carcinoma n cases: n/a n control: n/a	**Exposure Surrogate:** urine **Exposure Description:** urine samples collected for cases and controls and analyzed for urinary inorganic arsenic **Population-Level Exposure:** 5.27 µg/L median, 3.38-8.52 µg/L 25th percentile	**Outcome: squamous cell carcinoma (SCC)** ***ln-transformed total urinary arsenic, µg/L*** Exp. Level / n / adjOR / (CI) continuous / 323 / 1.37 / 1.04, 1.80 Stat Method: generalized linear model with a logit transform ***ln-transformed urinary inorganic arsenic, µg/L*** Exp. Level / n / adjOR / (CI) continuous / 323 / 1.2 / 0.97, 1.49 Stat Method: generalized linear model with a logit transform ***total urinary arsenic (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) <3.36 / 323 / 1 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		3.36 - <5.31 323 0.94 0.60, 1.45 ≥ 5.31 323 1.43 0.91, 2.27 Stat Method: generalized linear model with a logit transform
		urinary inorganic arsenic (tertiles), µg/L Exp. Level / n / adjOR / (CI) <0.23 323 1 n/a 0.23 - <0.45 323 0.97 0.63, 1.48 ≥ 0.45 323 1.27 0.82, 1.98 Stat Method: generalized linear model with a logit transform
Guo et al. (2006b) **Study Type:** case-control **Location:** Inner Mongolia (Wuyuan county) **Population:** adults with cutaneous lesions in arsenic-affected village n cases: 227 n control: 221	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water based on samples collected in triplicate from households using drinking water wells **Population-Level Exposure:** 0-1354 µg/L range	**Outcome: keratosis** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <50 NR 1 n/a 51-199 NR 1.46 0.61, 3.51 200-499 NR 0.92 0.45, 1.9 ≥ 500 NR 1.46 0.57, 3.75 Stat Method: logistic regression
		Outcome: pigment disorder ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <50 NR 1 n/a 51-199 NR 5.25 1.3, 83.24 200-499 NR 10.97 1.5, 79.95 ≥ 500 NR 10 1.39, 71.77 Stat Method: logistic regression
Guo et al. (2006a) **Study Type:** cross-sectional **Location:** China (Wuyuan county, Inner Mongolia) **Population:** residents of high and low arsenic-affected villages n cases: 109	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in water samples collected from all tube wells used by participants for at least 6 months in the last 20 years (several subjects shared the same wells); samples below the LOD were assigned 0 µg/L **Population-Level Exposure:** 50-197.3 µg/L range	**Outcome: skin lesions** ***well water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 50 NR 1 n/a 51-99 NR 15.5 1.53, 248.7 100-149 NR 16.1 3.73, 69.63 >150 NR 25.7 6.43, 102.87 Stat Method: Logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
n control: 32		
Guo et al. (2007) **Study Type:** cross-sectional **Location:** Mongolia region not available **Population:** residents of villages in the Hetao Plain, Inner Mongolia n cases: 680 n control: 189	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic samples were taken from 94 water sources, including wells; detection limit not specified, but authors note reliability of the method at <10 µg/L; arsenic exposure determined by location of village **Population-Level Exposure:** 50-1860 µg/L range	**Outcome: arsenic dermatosis** ***water arsenic concentration, µg/L*** arsenic not significantly associated with dermatosis
Hall et al. (2006) **Study Type:** case-control (nested) **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) participants randomly selected and members newly diagnosed with skin lesions n cases: 303 n control: 849	**Exposure Surrogate:** blood **Exposure Description:** arsenic concentration in whole blood collected and analyzed for each individual **Population-Level Exposure:** 1.6-63.9 µg/L range	**Outcome: skin lesions** ***arsenic concentration in blood (quintiles), µg/L*** Exp. Level / n / IRR / (CI) 1.6-5.4 / 41 / 1 / n/a 5.5-7.5 / 40 / 1.22 / 0.70, 2.12 7.6-10.4 / 51 / 1.21 / 0.69, 2.13 10.5-15 / 70 / 1.68 / 0.99, 2.86 15.1-63.9 / 101 / 2.54 / 1.51, 4.27 Stat Method: Cox proportional hazards models
	Exposure Surrogate: drinking water **Exposure Description:** arsenic concentration water samples from wells collected at baseline; time-weighted arsenic concentration based on drinking duration and well concentration (historical drinking source taken into account) **Population-Level Exposure:** 0.1-564 µg/L range	**Outcome: skin lesions** ***arsenic concentration in water (quintiles), µg/L*** Exp. Level / n / IRR / (CI) 0.1-7 / 48 / 1 / n/a 8-38 / 31 / 0.92 / 0.50, 1.67 39-94 / 48 / 1.27 / 0.73, 2.20 95-189 / 81 / 1.92 / 1.14, 3.24 190-564 / 95 / 2.5 / 1.52, 4.14 Stat Method: Cox proportional hazards models ***time-weighted arsenic concentration in water, µg/L*** Exp. Level / n / IRR / (CI) 0.1-7.9 / 40 / 1 / n/a 8.0-41 / 35 / 1.14 / 0.61, 2.11 42-94 / 51 / 1.44 / 0.81, 2.58 95-175 / 58 / 1.66 / 0.94, 2.93 176-564 / 101 / 2.85 / 1.66, 4.89

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases

Reference and Study Design	Exposure Measures	Results
		Stat Method: Cox proportional hazards models
	Exposure Surrogate: urine **Exposure Description:** individual total urinary arsenic concentration creatinine adjusted (urinary arsenic concentration not creatinine adjusted) **Population-Level Exposure:** 3-1230 µg/L range	**Outcome: skin lesions** ***arsenic concentration in urine (quintiles), µg/L*** Exp. Level / n / IRR / (CI) 3-35 / 36 / 1 / n/a 36-64 / 54 / 1.63 / 0.92, 2.89 65-113 / 54 / 1.73 / 0.99, 3.02 114 -201 / 68 / 2 / 1.13, 3.56 202-1230 / 91 / 3.16 / 1.73, 5.76 Stat Method: Cox proportional hazards models
Hashim et al. (2013) **Study Type:** cross-sectional **Location:** Cambodia (Mekong River basin) **Population:** residents of high, medium, and low arsenic-contaminated areas n cases: n/a n control: n/a	**Exposure Surrogate:** hair **Exposure Description:** arsenic concentration in hair samples collected from the nape of heads as close as possible to the scalp, washed, and analyzed for arsenic; arsenic recovery rate was 94.8%; median hair As levels: 0.090, 0.240, and 4.81 µg/g for Kampong Cham, Kratie, and Kandal, respectively **Population-Level Exposure:** not available	**Outcome: hyperkeratosis** ***hair arsenic concentration (0.5-µg/g cutoff), µg/g*** Exp. Level / n / Prev / (CI) <0.5 / 5 / 1.97 / n/a ≥ 0.5 / 41 / 16.2 / n/a Stat Method: prevalence rate; method of calculating significance not reported ***hair arsenic concentration (1-µg/g cutoff), µg/g*** Exp. Level / n / Prev / (CI) <1 / 14 / 4.94 / n/a ≥ 1 / 32 / 18.82 / n/a Stat Method: prevalence rate; method of calculating significance not reported **Outcome: hyperpigmentation** ***hair arsenic concentration (0.5-µg/g cutoff), µg/g*** Exp. Level / n / Prev / (CI) <0.5 / 7 / 2.76 / n/a ≥ 0.5 / 36 / 14.22 / n/a Stat Method: prevalence rate; method of calculating significance not reported ***hair arsenic concentration (1-µg/g cutoff), µg/g*** Exp. Level / n / Prev / (CI) <1 / 13 / 4.59 / n/a ≥ 1 / 30 / 17.64 / n/a Stat Method: prevalence rate; method of calculating significance not reported **Outcome: hypomelanosis** ***hair arsenic concentration (0.5-µg/g cutoff), µg/g***

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / Prev / (CI) <0.5 / 13 / 5.13 / n/a ≥ 0.5 / 63 / 24.9 / n/a Stat Method: prevalence rate; method of calculating significance not reported
		hair arsenic concentration (1-µg/g cutoff), µg/g Exp. Level / n / Prev / (CI) <1 / 21 / 7.42 / n/a ≥ 1 / 55 / 32.35 / n/a Stat Method: prevalence rate; method of calculating significance not reported
		Outcome: mee's lines
		hair arsenic concentration (0.5-µg/g cutoff), µg/g Exp. Level / n / Prev / (CI) <0.5 / 9 / 3.55 / n/a ≥ 0.5 / 24 / 9.48 / n/a Stat Method: prevalence rate; method of calculating significance not reported
		hair arsenic concentration (1-µg/g cutoff), µg/g Exp. Level / n / Prev / (CI) <1 / 14 / 4.94 / n/a ≥ 1 / 19 / 11.17 / n/a Stat Method: prevalence rate; method of calculating significance not reported
Hsu et al. (2013a) **Study Type:** cohort (prospective) **Location:** Taiwan (Peimen, Hsuechia, Putai, Ichu townships) **Population:** 3 separate subcohorts of residents of an arseniasis-endemic area n exposed: 1075 n reference: 535 n total: 2447	**Exposure Surrogate:** drinking water **Exposure Description:** lifetime cumulative arsenic exposure estimated using median arsenic concentration in village well where study subject lived and duration of exposure; arsenic concentrations in wells obtained from 2 investigations examining more than 38,565 wells across Taiwan; lifetime cumulative arsenic exposure (CAE) estimated using median arsenic concentration in village well where study subject lived and duration of exposure **Population-Level Exposure:** 1-20 mg/L - yr range	**Outcome: hyperkeratosis with or without hyperpigmentation**
		cumulative arsenic exposure, mg/L - yr difference between mean arsenic exposure of group with no arsenical skin lesions and this group was statistically significant; means not reported
		Outcome: hyperpigmentation only
		cumulative arsenic exposure, mg/L - yr difference between mean arsenic exposure of group with no arsenical skin lesions and this group was statistically significant; means not reported
		Outcome: skin cancer (Bowen's disease or NMSC) without hyperkeratosis
		cumulative arsenic exposure, mg/L - yr difference between mean arsenic exposure of group with no arsenical skin lesions and this group was statistically significant; means not reported

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		Outcome: skin cancer and hyperkeratosis ***cumulative arsenic exposure, mg/L - yr*** difference between mean arsenic exposure of group with no arsenical skin lesions and this group was statistically significant; means not reported
Hsueh et al. (1995) **Study Type:** cross-sectional **Location:** Taiwan (Putai Township) **Population:** residents of Homei, Fuhsin, and Hsingming villages n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative arsenic exposure index, based on arsenic concentration of well water (ppm) and duration of water consumption (years) for consecutive period of living in various villages **Population-Level Exposure:** 4-25 ppm-years range	**Outcome: skin cancer** ***cumulative arsenic exposure, ppm-years*** Exp. Level / n / adjOR / (CI) ≤ 4 / NR / 1 / n/a 5-24 / NR / 6.69 / 0.76, 59.17 =>25 / NR / 9.05 / 1.06, 77.27 Stat Method: multiple logistic regression; multivariate-adjusted
Hsueh et al. (1997) **Study Type:** cohort (prospective) **Location:** Taiwan (Putai township) **Population:** residents of Homei, Fushin, and Hsinming villages n total: 654	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration in artesian well water for each village obtained from a previous report (~1960s) **Population-Level Exposure:** 0-1.1 mg/L range	**Outcome: skin cancer** ***average well water arsenic concentration, mg/L*** Exp. Level / n / adjRR / (CI) 0 / 1 / 1 / n/a 0.01-0.7 / 12 / 3.3 / 0.42, 35.76 0.71-1.10 / 13 / 8.69 / 1.08, 65.5 unknown / 7 / 4.75 / 0.55, 40.35 Stat Method: multivariate adjusted relative risk using Cox's proportional hazards regression method
	Exposure Surrogate: drinking water **Exposure Description:** individual cumulative arsenic exposure based on average arsenic concentration in drinking water and cumulative arsenic exposure from well water; residential history and duration of well water consumption self-reported; arsenic concentration in artesian well water for each village was obtained from a previous report (~1960s) **Population-Level Exposure:** not available	**Outcome: skin cancer** ***cumulative arsenic exposure, mg/L - yr*** Exp. Level / n / adjRR / (CI) 0 / 1 / 1 / n/a 0.1-10.6 / 2 / 2.82 / 0.25, 31.87 0.7-17.7 / 5 / 2.61 / 0.30, 22.90 >17.7 / 18 / 7.58 / 0.95, 60.33 unknown / 7 / 5.14 / 0.59, 44.41 Stat Method: multivariate adjusted relative risk using Cox's proportional hazards regression method

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Karagas et al. (2001) **Study Type:** case-control **Location:** United States (NH) **Population:** individuals with or without squamous cell carcinoma or basal cell carcinoma n cases: 871 n control: 524	**Exposure Surrogate:** toenails **Exposure Description:** individual arsenic concentrations based on toenail samples; prior to analysis, nail samples were carefully washed to remove external contamination **Population-Level Exposure:** 0.009-2.57 µg/g range	**Outcome: basal cell carcinoma** ***toenail arsenic concentration, µg/g*** Exp. Level / n / adjOR / (CI) 0.009-0.089 / 281 / 1 / n/a 0.090-0.133 / 156 / 1.01 / 0.76, 1.35 0.134-0.211 / 92 / 1.06 / 0.74, 1.51 0.212-0.280 / 22 / 0.72 / 0.40, 1.31 0.281-0.344 / 10 / 0.75 / 0.31, 1.81 0.345-0.81 / 26 / 1.44 / 0.74, 2.81 Stat Method: logistic regression analysis **Outcome: Squamous cell carcinoma** ***toenail arsenic concentration, µg/g*** Exp. Level / n / adjOR / (CI) 0.009-0.089 / 155 / 1 / n/a 0.090-0.133 / 64 / 0.93 / 0.64, 1.34 0.134-0.211 / 33 / 0.98 / 0.61, 1.58 0.212-0.280 / 14 / 1.1 / 0.55, 2.21 0.281-0.344 / 5 / 1 / 0.33, 3.01 0.345-0.81 / 13 / 2.07 / 0.92, 4.66 Stat Method: logistic regression analysis
Knobeloch et al. (2006) **Study Type:** cross-sectional **Location:** United States (WI) **Population:** residents of 19 rural townships with arsenic contaminated private drinking wells n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** subjects submitted samples from drinking water source using provided kit **Population-Level Exposure:** 2 µg/L median, 1-3100 µg/L range	**Outcome: skin cancer** ***drinking water arsenic concentration, µg/L*** Exp. Level / n / adjOR / (CI) <1.0 / 15 / 1 / n/a 1-9.9 / 36 / 1.81 / 1.10, 3.14 ≥ 10 / 23 / 1.92 / 1.01, 3.68 Stat Method: multivariate logistic regression
Leonardi et al. (2012) **Study Type:** case-control	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic in drinking water derived from measurements at time of study and historical data when	**Outcome: basal cell carcinoma** ***cumulative inorganic arsenic dose concentration (quintiles), g*** Exp. Level / n / adjOR / (CI) 0-0.01 / NR / 1 / n/a 0.01-0.03 / NR / 1.09 / 0.72, 1.67

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Location: Hungary, Romania, Slovakia (Bács-Kiskun, Békés, Csongrád, and Jász-Nagykun-Szolnok counties (Hungary); Arad and Bihor counties (Romania); Banska Bystrica county (Slovakia)) **Population:** ASHRAM (Arsenic Health Risk Assessment and Molecular Epidemiology) study participants with chronic low-level arsenic exposure n cases: 529 n control: 540	available **Population-Level Exposure:** 0-4.46 g range	0.03-0.13 NR 1.46 0.93, 2.27 0.13-0.55 NR 1.76 1.02, 3.04 0.55-4.46 NR 2.63 1.45, 4.78 Stat Method: multivariable logistic regression model
	Exposure Surrogate: drinking water **Exposure Description:** arsenic in drinking water derived from measurements at time of study and historical data when available; peak daily dose rate calculated from the participant's residence with the highest water inorganic arsenic concentration **Population-Level Exposure:** 0-242.14 µg/day range	**Outcome: basal cell carcinoma** ***peak daily inorganic arsenic dose rate concentration (quintiles), µg/day*** Exp. Level n adjOR (CI) 0-0.73 NR 1 n/a 0.73-1.48 NR 0.91 0.59, 1.39 1.48-9.09 NR 1.55 1, 2.41 9.09-32.23 NR 1.76 1.01, 3.07 32.23-242.14 NR 2.5 1.39, 4.49 Stat Method: multivariable logistic regression model
	Exposure Surrogate: drinking water **Exposure Description:** drinking water samples collected at time of study or historical data utilized when available **Population-Level Exposure:** 1.2 µg/L median, 0.7-13.8 µg/L 25th percentile	**Outcome: basal cell carcinoma** ***lifetime time-weighted average inorganic arsenic concentration (quintiles), µg/L*** Exp. Level n adjOR (CI) 0-0.68 NR 1 n/a 0.68-0.98 NR 1.39 0.89, 2.19 0.98-7 NR 1.2 0.77, 1.88 7.1-19.43 NR 1.73 0.97, 3.11 19.54-167.29 NR 3.03 1.70, 5.41 Stat Method: multivariable logistic regression model
Lewis et al. (1999) **Study Type:** cohort (retrospective) **Location:** United States (Millard County, Utah) **Population:** male and female members of Latter-day Saints church wards n exposed: 2203 n total: 2203	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentrations in drinking water determined from Utah state records and an EPA study; arsenic exposure index score calculated individually based on number of years residence in each community and median drinking water arsenic concentration in community **Population-Level Exposure:** 3.5-620 ppb-years range	**Outcome: melanoma** ***cumulative arsenic exposure (females), ppb-years*** Exp. Level n SMR (CI) <1000 NR 5.3 n/a 1000-4999 NR NR n/a ≥ 5000 NR NR n/a Stat Method: standardized mortality ratios ***cumulative arsenic exposure (males), ppb-years*** Exp. Level n SMR (CI) <1000 NR 0.72 n/a 1000-4999 NR 0.79 n/a ≥ 5000 NR 1.06 n/a Stat Method: standardized mortality ratios

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Li et al. (2013a) **Study Type:** cross-sectional **Location:** China (Tuoketuo County, Inner Mongolia) **Population:** residents exposed to arsenic in drinking water n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration of each tube well measured and provided by local public health government; cumulative arsenic exposure (CAE) calculated for each subject as: concentration in tube well that subject used in his/her residential duration multiplied by duration of water consumption **Population-Level Exposure:** 0-760 µg/L range	**Outcome: skin lesions** ***water arsenic concentration, µg/L*** 84 patients with skin lesions found in the >50-µg/L group with symptoms of hyperpigmentation and/or depigmentation on the trunk
Lindberg et al. (2008) **Study Type:** case-control (nested) **Location:** Bangladesh (Matlab) **Population:** selected members of Health and Demographic Surveillance System (HDSS) n cases: 504 n control: 528	**Exposure Surrogate:** drinking water **Exposure Description:** cumulative exposure calculated by summing up arsenic concentration multiplied by number of years of usage for all water sources used since 1970 **Population-Level Exposure:** 1639-4107 µg/L-year range	**Outcome: Skin lesion cases** ***cumulative arsenic exposure concentration, µg/L-year*** Exp. Level / n / adjOR / (CI) ≤ 1639 / NR / 1 / n/a 1639-4107 / NR / 1.3 / 0.9, 2.0 >4107 / NR / 3.8 / 2.7, 5.5 Stat Method: Multivariate logistic regression analysis
	Exposure Surrogate: drinking water **Exposure Description:** self-reported water consumption history and water sources used during each calendar year since 1970 (or birth, if later than 1970); water samples from all functional tube wells collected; for surface water drinking source, arsenic concentration set to 0 µg/L; nonfunctioning wells historical exposure reconstructed using average tube well arsenic concentration of village as proxy **Population-Level Exposure:** 80-181 µg/L range	**Outcome: Skin lesion cases** ***average lifetime arsenic exposure concentration (tertiles), µg/L*** Exp. Level / n / adjOR / (CI) ≤ 80 / NR / 1 / n/a 80-181 / NR / 1.4 / 0.98, 2.1 >181 / NR / 3.4 / 2.4, 4.8 Stat Method: Multivariate logistic regression analysis
	Exposure Surrogate: urine	**Outcome: Skin lesion cases** ***percent urinary DMA metabolite concentration,***

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
	Exposure Description: individual spot urine samples analyzed for arsenic speciation **Population-Level Exposure:** 9.5-13 % range	***%*** Exp. Level / n / adjOR / (CI) ≤ 76 / NR / 1 / n/a 76-82 / NR / 0.39 / 0.28, 0.55 >82 / NR / 0.41 / 0.28, 0.60 Stat Method: Multivariate logistic regression analysis
		percent urinary inorganic arsenic metabolite concentration, % Exp. Level / n / adjOR / (CI) ≤ 9.5 / NR / 1 / n/a 9.5-13 / NR / 0.93 / 0.65, 1.3 >13 / NR / 1.8 / 1.3, 2.6 Stat Method: Multivariate logistic regression analysis
		percent urinary MA metabolite concentration, % Exp. Level / n / adjOR / (CI) ≤ 7.9 / NR / 1 / n/a 7.9-12 / NR / 1.1 / 0.74, 1.7 >12 / NR / 2.8 / 1.9, 4.2 Stat Method: Multivariate logistic regression analysis
	Exposure Surrogate: urine **Exposure Description:** spot urine samples collected from individuals and analyzed for arsenic metabolites **Population-Level Exposure:** 51-124 µg/L range	**Outcome: Skin lesion cases** ***sum of arsenic metabolites concentration in urine, µg/L*** Exp. Level / n / adjOR / (CI) ≤ 51 / NR / 1 / n/a 51-124 / NR / 0.72 / 0.51, 1.0 >124 / NR / 1.5 / 1.1, 2.0 Stat Method: Multivariate logistic regression analysis
Maden et al. (2011) **Study Type:** cross-sectional **Location:** Nepal (Nawalparasi district) **Population:** residents of program areas of	**Exposure Surrogate:** drinking water **Exposure Description:** tubewell samples collected from individual households; total water arsenic calculated using exposure duration (based on total age of tubewell and years of residence); exposure duration counted from 5 years of age **Population-Level Exposure:**	**Outcome: arsenicosis cases** ***time weighted total arsenic concentration in drinking water, µg/L*** Exp. Level / n / adjBeta / (CI) continuous / NR / 2.132 / n/a Stat Method: binomial logistic regression; stepwise backward strategic method following parsimonious model

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Filters for Families (FFF) in Jahada, Sarawal, Sunawal, Sukrauli, and Swati (development communities) or Ramgram (municipality) n cases: 120 n control: n/a	50-50 µg/L range	
Mazumder et al. (1998) **Study Type:** cross-sectional **Location:** India (West Bengal) **Population:** residents of highly contaminated South 24 Parganas n cases: 7683 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** water samples collected from private and public tube wells used for drinking and cooking for each household; daily dose per body weight computed by multiplying water arsenic concentration by estimated daily water intake (based on interview) and dividing by body weight **Population-Level Exposure:** 0-73.9 µg/kg-day range	**Outcome: hyperpigmentation** ***daily arsenic dose per body weight concentration (males and females), µg/kg-day*** Exp. Level / n / SMR / (CI) continuous / NR / 1.2 / 0.8, 1.8 Stat Method: Poisson distribution **Outcome: keratosis** ***daily arsenic dose per body weight concentration (males and females), µg/kg-day*** Exp. Level / n / SMR / (CI) continuous / NR / 1.6 / 1, 2.4 Stat Method: Poisson distribution
	Exposure Surrogate: drinking water **Exposure Description:** water samples collected from private and public tubewells used for drinking and cooking for each household **Population-Level Exposure:** 0-3400 µg/L range	**Outcome: hyperpigmentation** ***arsenic concentration in drinking water (females), µg/L*** Exp. Level / n / Prev / (CI) <50 / NR / 0.3 / n/a 50 - 99 / NR / 0.8 / n/a 100 - 149 / NR / 5.7 / n/a 150 - 199 / NR / 5.1 / n/a 200 - 349 / NR / 6.5 / n/a 350 - 499 / NR / 9.5 / n/a 500 - 799 / NR / 5.3 / n/a ≥ 800 µg/L / / / / ≥ 800 / NR / 11.5 / n/a Stat Method: Chi-squared distribution ***arsenic concentration in drinking water (males), µg/L*** Exp. Level / n / Prev / (CI) <50 / NR / 0.4 / n/a 50 - 99 / NR / 3.2 / n/a 100 - 149 / NR / 11 / n/a 150 - 199 / NR / 7.8 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		200 - 349 NR 13.1 n/a 350 - 499 NR 15.7 n/a 500 - 799 NR 13.8 n/a ≥ 800 NR 22.7 n/a Stat Method: Chi-squared distribution
		Outcome: keratosis
		arsenic concentration in drinking water (females), µg/L Exp. Level / n / Prev / (CI) <50 NR 0 n/a 50 - 99 NR 0.4 n/a 100 - 149 NR 1.2 n/a 150 - 199 NR 2.3 n/a 200 - 349 NR 2 n/a 350 - 499 NR 2.7 n/a 500 - 799 NR 3.1 n/a ≥ 800 µg/L ≥ 800 NR 8.3 n/a Stat Method: Chi-squared distribution
		arsenic concentration in drinking water (males), µg/L Exp. Level / n / Prev / (CI) <50 NR 0.2 n/a 50 - 99 NR 1.5 n/a 100 - 149 NR 1.6 n/a 150 - 199 NR 4.7 n/a 200 - 349 NR 4.9 n/a 350 - 499 NR 9 n/a 500 - 799 NR 8.9 n/a ≥ 800 NR 10.7 n/a Stat Method: Chi-squared distribution
McDonald et al. (2007) **Study Type:** case-control **Location:** Bangladesh (rural Bangaldesh) **Population:** women living in villages serviced and selected	**Exposure Surrogate:** drinking water **Exposure Description:** tube well samples collected from sources currently used by subjects (three samples collected/source, highest concentration used) **Population-Level Exposure:** 0-166 µg/L range	**Outcome: Skin lesions** ***arsenic concentration in drinking water, µg/L*** Exp. Level / n / OR / (CI) 0-10 NR 1 n/a 11-50 NR 1.33 0.77, 2.28 >51 NR 2.96 1.02, 8.59 Stat Method: Conditional logistic regression

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
by Gonoshashthaya Kendra n cases: 155 n control: 155		
Melkonian et al. (2011) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** male Health Effects of Arsenic Longitudinal Study (HEALS) participants 6 year follow-up n exposed: 613 n reference: 3378 n total: 3991	**Exposure Surrogate:** drinking water **Exposure Description:** exposure characterized using well-water arsenic concentration, daily intake of arsenic from drinking water based on self-report and primary drinking water source; samples GFAA LOD (5 µg/L) reanalyzed with inductively coupled plasma mass spectrometry **Population-Level Exposure:** 0.1-200.1 µg/L range	**Outcome: skin lesions** ***well water arsenic concentration (quintiles), µg/L*** Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.08 / 0.85, 1.38 50.1-100 / NR / 1.52 / 1.19, 1.93 100.1-200 / NR / 1.86 / 1.48, 2.32 ≥ 200.1 / NR / 2.69 / 2.16, 3.35 Stat Method: Multivariate log-linear regression
	Exposure Surrogate: urine **Exposure Description:** exposure characterized using creatinine-adjusted urinary total arsenic concentration; spot urine samples were obtained from 3,804 of the 3,991 subjects **Population-Level Exposure:** 89-405 µg/g-creatinine range	**Outcome: skin lesions** ***Urinary total arsenic (quintiles), µg/g-creatinine*** Exp. Level / n / HR / (CI) ≤ 89 / NR / 1 / n/a 89.1-159 / NR / 0.89 / 0.70, 1.14 159.1-245 / NR / 1.28 / 1.02, 1.60 245.1-405 / NR / 1.38 / 1.10, 1.73 >405 / NR / 1.86 / 1.50, 2.31 Stat Method: Multivariate log-linear regression
Mitra et al. (2002) **Study Type:** cross-sectional **Location:** Bangladesh (Barisal) **Population:** dermatology outpatients of Sher-e-Bangla Medical College Hospital n cases: 123 n control: 27	**Exposure Surrogate:** drinking water **Exposure Description:** water samples from current tube wells used by the study participants examined using standard methods; exposure dose based on self reported information of duration of use of water at source **Population-Level Exposure:** 0.5 mg/L mean 0.21SD	**Outcome: mild skin disease** ***drinking water arsenic concentration, mg/L*** Exp. Level / n / Prev / (CI) ≤ 0.50 / 22 / 82 / n/a 0.51-0.99 / 4 / 15 / n/a ≥ 1.00 / 1 / 4 / n/a Stat Method: Chi-squared test ***drinking water arsenic concentration, mg/L*** Exp. Level / n / mean / (CI) continuous / NR / 0.43 / n/a Stat Method: Mann-Whitney U-test ***exposure dose (arsenic level x exposure time) mg/L - yr, mg/L*** Exp. Level / n / mean / (CI) mg/L-yr / NR / 7.66 / n/a

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: Mann-Whitney U-test **Outcome: moderate and severe skin disease** ***drinking water arsenic concentration, mg/L*** Exp. Level / n / Prev / (CI) ≤ 0.50 / NR / 66 / n/a 0.51-0.99 / NR / 29 / n/a ≥ 1.00 / NR / 5 / n/a Stat Method: Chi-squared test ***drinking water arsenic concentration, mg/L*** Exp. Level / n / mean / (CI) continuous / NR / 0.52 / n/a Stat Method: Mann-Whitney U-test ***exposure dose (arsenic level x exposure time) mg/L - yr, mg/L*** Exp. Level / n / mean / (CI) mg/L-yr / NR / 8.29 / n/a Stat Method: Mann-Whitney U-test
Mosaferi et al. (2008) **Study Type:** cross-sectional **Location:** Iran (Kurdistan province) **Population:** residents exposed to arsenic-contaminated water in Bijar County n cases: 752 n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** total lifetime intake of arsenic, based on arsenic levels measured in villages once each season for 4 testings) in the villages to obtain mean annual concentration; questionnaires used to determine water source, consumption history, and changes over time; concentration, questionnaires, interviews and historical data used to calculate total lifetime intake of arsenic **Population-Level Exposure:** 0-3 g range	**Outcome: hyperkeratosis** ***total lifetime intake of arsenic, g*** Exp. Level / n / adjOR / (CI) continuous / 49 / 1.14 / 1.039, 1.249 Stat Method: Logistic regression **Outcome: hyperpigmentation** ***total lifetime intake of arsenic, g*** Exp. Level / n / adjOR / (CI) continuous / 20 / 1.254 / 1.112, 1.416 Stat Method: Logistic regression
Pei et al. (2013) **Study Type:** cross-sectional **Location:** China (Shanxi province)	**Exposure Surrogate:** urine **Exposure Description:** urinary arsenic concentration, spot morning urine samples collected; each sample subjected to two replicate analyses **Population-Level Exposure:**	**Outcome: skin lesions** ***urinary arsenic concentration, µg/g-creatinine*** Exp. Level / n / adjOR / (CI) continuous / NR / 3.895 / 0.497, 30.52 Stat Method: multiple regression analysis; Spearman's rank correlation coefficient

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Population: residents of arsenic endemic rural region in Datong n cases: 75 n control: 12	not available	
Pesola et al. (2012) **Study Type:** cross-sectional **Location:** Bangladesh (Araihazar) **Population:** Health Effects of Arsenic Longitudinal Study (HEALS) participants n cases: n/a n control: n/a	**Exposure Surrogate:** drinking water **Exposure Description:** well water arsenic concentration **Population-Level Exposure:** 7-179 µg/L range	**Outcome: skin lesions** ***well water arsenic concentration (quintiles), µg/L*** Exp. Level / n / adjOR / (CI) <7 / NR / 1 / n/a 7 -<39 / NR / 1.8 / 1.02, 3.16 39 -<91 / NR / 2.79 / 1.62, 4.78 91 -<179 / NR / 3.09 / 1.82, 5.23 ≥ 179 / NR / 3.94 / 2.36, 6.58 Stat Method: logistic regression; Chi-squared test for trend
Pierce et al. (2011) **Study Type:** cohort (prospective) **Location:** Bangladesh (Araihazar) **Population:** HEALS participants in Araihazar, Bangladesh 2000-2009 n total: 9677	**Exposure Surrogate:** drinking water **Exposure Description:** well water arsenic concentrations; exposure categorized into quintiles with adjustment to corresponded to WHO guideline (10 µg/L) and Bangladesh national standard (50 µg/L); participants categorized by quartiles of dietary intakes for 3 categories(gourd and root, vegetable, and animal protein) as measured by food frequency questionnaire **Population-Level Exposure:** 0.1-200.1 µg/L range	**Outcome: incident skin lesions** ***water arsenic concentration by dietary pattern: gourd and root quartile 1, µg/L*** Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.44 / 0.89, 2.34 50.1-100 / NR / 2.26 / 1.42, 3.6 100.1-200 / NR / 3.5 / 2.34, 5.25 >200 / NR / 5.3 / 3.19, 8.81 Stat Method: multivariate regression ***water arsenic concentration by dietary pattern: gourd and root quartile 2, µg/L*** Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.14 / 0.75, 1.75 50.1-100 / NR / 1.65 / 1.07, 2.57 100.1-200 / NR / 1.8 / 1.23, 2.65 >200 / NR / 3.19 / 2.00, 5.09 Stat Method: multivariate regression ***water arsenic concentration by dietary pattern: gourd and root quartile 3, µg/L***

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.22 / 0.45, 1.99 50.1-100 / NR / 1.58 / 0.97, 2.59 100.1-200 / NR / 2.17 / 1.45, 3.29 >200 / NR / 2.8 / 1.61, 4.89 Stat Method: multivariate regression
		water arsenic concentration by dietary pattern: gourd and root quartile 4, µg/L Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 0.76 / 0.52, 1.4 50.1-100 / NR / 1.21 / 0.74, 1.98 100.1-200 / NR / 1.43 / 0.93, 2.2 >200 / NR / 3.3 / 1.92, 5.67 Stat Method: multivariate regression
		water arsenic concentration by dietary pattern: vegetable quartile 1, µg/L Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 0.96 / 0.55, 1.68 50.1-100 / NR / 1.48 / 0.88, 2.48 100.1-200 / NR / 2.63 / 1.69, 4.12 >200 / NR / 5.68 / 3.39, 9.52 Stat Method: multivariate regression
		water arsenic concentration by dietary pattern: vegetable quartile 2, µg/L Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.36 / 0.89, 2.09 50.1-100 / NR / 1.75 / 1.14, 2.7 100.1-200 / NR / 1.89 / 1.26, 2.83 >200 / NR / 3.72 / 2.23, 6.21 Stat Method: multivariate regression
		water arsenic concentration by dietary pattern: vegetable quartile 3, µg/L Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 1.39 / 0.87, 2.24 50.1-100 / NR / 1.66 / 1.02, 2.71 100.1-200 / NR / 2.28 / 1.53, 3.4 >200 / NR / 2.9 / 1.69, 5

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		Stat Method: multivariate regression ***water arsenic concentration by dietary pattern: vegetable quartile 4, µg/L*** Exp. Level / n / HR / (CI) 0.1-10 / NR / 1 / n/a 10.1-50 / NR / 0.82 / 0.49, 1.36 50.1-100 / NR / 1.78 / 1.13, 2.79 100.1-200 / NR / 1.96 / 1.35, 2.85 >200 / NR / 2.39 / 1.43, 3.97 Stat Method: multivariate regression
Rahman et al. (2006a) **Study Type:** case-control **Location:** Bangladesh (Matlab) **Population:** individuals drinking water from arsenic-contaminated tube wells n cases: 504 n control: 1830	**Exposure Surrogate:** drinking water **Exposure Description:** average arsenic exposure concentration; individuals provided information on water consumption history from 1970 (or birth if after 1970); samples were obtained from all functioning tube wells, with village concentration used as proxy if well samples unavailable; surface waters assigned a concentration of 0 µg/L; arsenic concentrations were imputed for migrants **Population-Level Exposure:** 10-300 µg/L range	**Outcome: as-related skin lesions** ***average arsenic exposure concentration (quintiles; females), µg/L*** Exp. Level / n / adjOR / (CI) <10 / 12 / 1 / n/a 10-49 / 15 / 1.66 / 0.65, 4.24 50-149 / 65 / 3.06 / 1.39, 6.74 150-299 / 84 / 4.08 / 1.86, 8.93 ≥ 300 / 56 / 6.88 / 3.06, 15.5 Stat Method: multivariate logistic regression ***average arsenic exposure concentration (quintiles;males), µg/L*** Exp. Level / n / adjOR / (CI) <10 / 13 / 1 / n/a 10-49 / 38 / 3.25 / 1.43, 7.38 50-149 / 59 / 2.28 / 1.04, 4.98 150-299 / 110 / 5.41 / 2.52, 1.62 ≥ 300 / 52 / 9.56 / 4.20, 21.8 Stat Method: multivariate logistic regression
	Exposure Surrogate: drinking water **Exposure Description:** individuals provided information on water consumption history from 1970 (or birth if after 1970); reported information was validated using household economic surveys with information of sources of drinking water; samples were obtained from all functioning tube wells; if tube well samples unavailable village concentration was used as proxy; surface	**Outcome: as-related skin lesions** ***cumulative arsenic exposure concentration (females), µg/L-year*** Exp. Level / n / adjOR / (CI) <1000 / 22 / 1 / n/a 1000-4999 / 78 / 1.94 / 1.1, 3.42 5000-9999 / 87 / 4.5 / 2.54, 7.99 >10000 / 45 / 9.19 / 4.77, 17.7 Stat Method: multivariate logistic regression ***cumulative arsenic exposure concentration (males), µg/L-year*** Exp. Level / n / adjOR / (CI)

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
	waters were assigned a concentration of 0 µg/L; arsenic concentrations were imputed for migrants **Population-Level Exposure:** 1000-10000 µg/L-year range	<1000 37 1 n/a 1000-4999 75 1.05 0.65, 1.68 5000-9999 119 4.5 2.80, 7.22 >10000 41 10.4 5.27, 20.5 NR NR n/a ≥ 300 Stat Method: multivariate logistic regression
Ranft et al. (2003) **Study Type:** case-control **Location:** Slovakia region not available **Population:** Residents of Prievidza District living in vicinity of coal-burning power plant n cases: 210 n control: 201	**Exposure Surrogate:** soil **Exposure Description:** arsenic concentrations in soil and house dust collected from random sample of participants' households **Population-Level Exposure:** 0.7-139 µg/g range	**Outcome: nonmelanoma skin cancer** ***arsenic concentration in soil, µg/g*** Exp. Level n stepwise multiple regression (CI) means ratio NR 1.18 n/a Stat Method: stepwise regression analysis
	Exposure Surrogate: urine **Exposure Description:** urinary arsenic concentration; spot urine samples provided at interview; population-level exposure numbers reported are for creatinine-corrected sum As **Population-Level Exposure:** 6.07 µg/L geo mean, 1.79SD, 6.07-1.79 µg/L	**Outcome: nonmelanoma skin cancer** ***urinary arsenic concentration, µg/L*** Exp. Level n stepwise multiple regression (CI) continuous 210 1.12 n/a Stat Method: stepwise regression analysis
Seow et al. (2012) **Study Type:** cohort (prospective) **Location:** Bangladesh (Pabna) **Population:** individuals with arsenic-related skin lesions n total: 550	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration in water, water samples collected from each participant's primary drinking source and data collected on drinking habits, water source, length of use; baseline data collected 2001-2003; samples collected again at follow up (2009-2011) **Population-Level Exposure:** not available	**Outcome: skin lesion recovery** ***log10 water arsenic concentration (decrease between baseline and follow-up), µg/L*** Exp. Level n adjOR (CI) continuous NR 1.22 0.85, 1.78 Stat Method: logistic regression ***log10 water arsenic concentration (baseline), µg/L*** Exp. Level n adjOR (CI) continuous NR 0.59 0.41, 0.81 Stat Method: logistic regression **Outcome: skin lesion severity reduction** ***log10 water arsenic concentration (decrease***

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
		between baseline and follow-up), µg/L Exp. Level n adjBeta (CI) continuous NR -0.7 -2.18, 0.78 Stat Method: linear regression GEE
		log10 water arsenic concentration (baseline), µg/L Exp. Level n adjBeta (CI) continuous NR -1.34 -2.85, 0.18 Stat Method: linear regression GEE
	Exposure Surrogate: toenails **Exposure Description:** arsenic concentration in nail clippings collected from each participant and sonicated to remove contaminants; baseline data collected 2001-2003; samples collected again at follow up (2009-2011) **Population-Level Exposure:** not available	**Outcome: skin lesion recovery**
		log10 toenail arsenic concentration (baseline), µg/g Exp. Level n adjOR (CI) continuous NR 0.2 0.08, 0.44 Stat Method: logistic regression
		log10 toenail arsenic concentration (decrease between baseline and follow-up), µg/g Exp. Level n adjOR (CI) continuous NR 4.49 1.94, 11.1 Stat Method: logistic regression
		Outcome: skin lesion severity reduction
		log10 toenail arsenic concentration (baseline), µg/g Exp. Level n adjBeta (CI) continuous NR -0.09 -3.41, 3.22 Stat Method: linear regression GEE
		log10 toenail arsenic concentration (decrease between baseline and follow-up), µg/g Exp. Level n adjBeta (CI) continuous NR -5.22 -8.61, -1.82 Stat Method: linear regression GEE
Xia et al. (2009) **Study Type:** cross-sectional **Location:** China (Bayingnormen, Shahai village)	**Exposure Surrogate:** drinking water **Exposure Description:** arsenic concentration in drinking water; exposure calculated from single well water sample collected from each household	**Outcome: Skin lesions**
		drinking water arsenic concentration, µg/L Exp. Level n adjOR (CI) 0-5 NR 1 n/a 5.1-10 NR 2.52 1.47, 4.30 10.1-20 NR 2.83 1.773, 4.525 20.1-50 NR 3.94 2.78, 5.59 50.1-100 NR 6.03 4.05, 8.97 100.1-300 NR 8.83 5.77, 13.51

Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases		
Reference and Study Design	**Exposure Measures**	**Results**
Population: adults and children living in arseniasis-endemic village n cases: 11416 n control: n/a	**Population-Level Exposure:** 37.94 µg/L mean	>300 NR 7.94 2.73, 23.12 Stat Method: logistic regression model

--: not reported; n: number of cases (when presented in Results column)

5.16.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Skin Diseases

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6 SUMMARY OF RISK OF BIAS EVALUATIONS FOR INORGANIC ARSENIC ANIMAL STUDIES

6.1 Risk of Bias Overview - Developmental Effects including Neurodevelopmental

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Aggarwal et al. (2007)	P	+	+	n/a	+	+	+	+	+	++	-	+	+	+	++	++
Ahmad et al. (2013)	P	-	-	n/a	++	-	++	+	+	++	-	+	++	+	-	++
Chattopadhyay et al. (2002)	S	-	-	n/a	-	+	+	+	+	-	+	n/a	-	-	++	-
Colomina et al. (1997)	P	+	+	n/a	++	+	++	+	+	-	-	+	+	-	++	++
Gandhi et al. (2012)	P	-	-	n/a	-	+	+	+	+	++	++	+	-	++	+	+
Markowski et al. (2012)	P	++	+	n/a	++	+	++	+	+	+	++	+	+	++	++	++
Martinez et al. (2008)	P	-	-	n/a	+	+	++	+	+	-	+	+	+	+	+	+
Martinez-Finley et al. (2009)	P	-	-	n/a	-	+	++	+	+	-	++	+	++	+	++	++
Nagaraja and Desiraju (1993)	P	-	-	n/a	+	+	+	+	+	-	+	-	-	-	-	+
Nagymajtenyi et al. (1985)	P	-	-	n/a	+	+	+	+	+	+	-	+	-	-	++	-
Ramsey et al. (2013c)	P	-	-	n/a	+	+	+	+	+	-	+	+	+	+	+	++

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Rodríguez et al. (2002)	P	-	-	n/a	+	+	+	+	+	+	+	+	-	+	++	++
Xi et al. (2009)	P	+	+	n/a	-	+	++	+	+	-	-	+	+	+	++	++

6.2 Risk of Bias Overview - Immune System and Lymphatic Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Das et al. (2012b)	P	++	+	n/a	+	+	+	+	+	-	+	+	+	+	+	++
Kozul et al. (2009)	P	-	-	n/a	+	+	++	+	+	-	+	+	-	+	++	++
Nain and Smits (2012)	P	+	+	n/a	+	+	+	+	+	-	++	+	+	++	+	++
Ramsey et al. (2013b)	P	-	-	n/a	+	+	+	+	+	++	++	+	-	+	++	++
Sankar et al. (2013)	P	+	+	n/a	+	+	+	+	+	++	+	+	-	++	+	++
Stępnik et al. (2009)	P	-	-	n/a	+	+	++	+	+	++	+	+	-	+	++	++
Tokar et al. (2010b)	P	+	+	n/a	+	+	+	+	+	++	++	+	-	+	+	++
Waalkes et al. (2003)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	+	+	++
Waalkes et al. (2006a)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	++	+	++
Waalkes et al. (2006b)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	++	+	++

6.3 Risk of bias Overview - Liver Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Nain and Smits (2012)	P	+	+	n/a	+	+	+	+	+	-	++	+	+	++	+	++
Stępnik et al. (2009)	P	-	-	n/a	+	+	++	+	+	++	+	+	-	+	++	++
Tokar et al. (2010b)	P	+	+	n/a	+	+	+	+	+	++	++	+	-	+	+	++
Tokar et al. (2011)	P	-	-	n/a	++	+	+	+	+	++	++	+	+	++	+	++
Tokar et al. (2012)	P	+	+	n/a	+	+	+	+	+	++	++	+	+	++	+	++
Waalkes et al. (2003)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	+	+	++
Waalkes et al. (2004b)	P	+	+	n/a	++	+	++	+	+	+	++	+	-	++	++	++
Waalkes et al. (2006a)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	++	+	++
Waalkes et al. (2006b)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	++	+	++

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7 EVIDENCE TABLES FOR INORGANIC ARSENIC ANIMAL STUDIES

7.1 Summary of Observational Animal Studies for Health Effect Category: Developmental Effects including Neurodevelopmental

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental			
Reference and Dosing Protocol	**Results by Endpoint**		
(Aggarwal et al., 2007) **Dosing Design:** reproductive/developmental **Chemical:** Sodium Arsenite - NaAsO2 **Species and Strain:** rat, Wistar **Route of Exposure:** oral - gavage **Administered Doses:** F1, combined (73-90/group): 0, 1 mg/kg /day **Dosing Description:** P0 dams dosed daily from GD6 through GD15	**crown-rump length**		
	Generation, Sex	Dose(n)	Response (cm±SE)
	F1, Combined	0 (89)	3.74(±0.1)
		1 (72)	3.54(±0.09)
	no statistically significant effect on crown-rump length observed up to 1 mg/kg/day exposure		
	fetal weight		
	Generation, Sex	Dose(n)	Response (g±SE)
	F1, Combined	0 (89)	4.12(±0.08)
		1 (72)	4.05(±0.1)
	no statistically significant effect on fetal weight observed up to 1 mg/kg/day exposure		
	gross anomalies		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (90)	8.89
		1 (73)	32.88*
	skeletal anomalies		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (48)	12.5
		1 (38)	21.05*
	visceral anomalies		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (42)	0
		1 (35)	0
	no statistically significant effect on visceral anomalies observed up to 1mg/kg/day exposure		
(Ahmad et al., 2013) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenate - Na2HAsO4 **Species and Strain:** mice, Swiss Webster **Route of Exposure:** oral - water **Administered Doses:** F1, combined (21/group): 0, 40 mg/kg body weight/day; F1, male (NR): 0, 40	**cliff avoidance**		
	Generation, Sex		
	F1, Combined		
	40 mg/kg-bw/day arsenic had significant ($p<0.05$ or $p<0.01$) suppressive effect on mean cliff avoidance at each observation (PND 1-21)		
	immobility duration		

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental			
Reference and Dosing Protocol	**Results by Endpoint**		
mg/kg body weight/day **Dosing Description:** P0 dams dosed daily from GD0 through PND15	Generation, Sex	Dose(n)	Response (seconds)
	F1, Male	0 (10)	73.5
		40 (10)	208*
	movement duration		
	Generation, Sex	Dose(n)	Response (seconds)
	F1, Male	0 (10)	226.5
		40 (10)	92.5*
	number of rears		
	Generation, Sex	Dose(n)	Response (median)
	F1, Male	0 (10)	15
		40 (10)	5*
	number of squares crossed		
	Generation, Sex	Dose(n)	Response (median)
	F1, Male	0 (10)	371
		40 (10)	128*
	number of wall rears		
	Generation, Sex	Dose(n)	Response (median)
	F1, Male	0 (10)	33
		40 (10)	9*
	number of washes		
	Generation, Sex	Dose(n)	Response (median)
	F1, Male	0 (10)	6
		40 (10)	7
	righting reflex		
	Generation, Sex F1, Combined 40 mg/kg-bw/day arsenic had significant ($p<0.05$ or $p<0.01$) suppressive effect on mean righting reflex at each observation (PND 1-21)		
	rotating reflex		
	Generation, Sex F1, Combined 40 mg/kg-bw/day arsenic had significant ($p<0.05$ or $p<0.01$) suppressive effect on mean rotating reflex at each observation (PND 1-21)		
(Gandhi et al., 2012) **Dosing Design:** reproductive/developmental **Chemical:** arsenic **Species and Strain:** rat, Wistar **Route of Exposure:** oral - gavage **Administered Doses:** F1, combined (20/group): 0, 1.5, 3, 4.5 mg/kg	**cliff avoidance observed**		
	Generation, Sex	Dose(n)	Response (PND±SE)
	F1, Combined	0 (20)	11(±0.3)
		1.5 (20)	11(±0.25)
		3 (20)	10.8(±1.27)
		4.5 (20)	10.76(±1.24)

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental	
Reference and Dosing Protocol	**Results by Endpoint**
Dosing Description: P0 dams dosed daily from GD8 through PND0	no statistically significant effect on cliff avoidance observed up to 4.5 mg/kg
	developmental milestones
	Generation, Sex F1, Combined no statistically significant effect on day of pinna detachment, incisors eruption, fur development, eye opening, ear opening, testes decent, or vaginal opening observed up to 4.5 mg/kg
	ear twitch observed
	Generation, Sex / Dose(n) / Response (PND±SE) F1, Combined / 0 (20) / 24.48(±0.18) 1.5 (20) / 24.44(±0.2) 3 (20) / 24.6(±0.91) 4.5 (20) / 24.76(±0.92) no statistically significant effect on ear twitch observed up to 4.5 mg/kg
	free fall righting observed
	Generation, Sex / Dose(n) / Response (PND±SE) F1, Combined / 0 (20) / 24.44(±0.25) 1.5 (20) / 24.36(±0.88) 3 (20) / 24.48(±0.26) 4.5 (20) / 24.36(±0.29) no statistically significant effect on free fall righting observed up to 4.5 mg/kg
	limb withdrawal reflexes observed
	Generation, Sex / Dose(n) / Response (PND±SE) F1, Combined / 0 (20) / 23.6(±0.91) 1.5 (20) / 24(±0.18) 3 (20) / 23.56(±0.17) 4.5 (20) / 23.3(±1) no statistically significant effect on limb withdrawal reflexes observed up to 4.5 mg/kg
	morphological anomalies
	Generation, Sex F1, Combined no statistically significant effect on morphological anomalies observed up to 4.5 mg/kg
	muscular grip strength
	Generation, Sex / Dose(n) / Response (sec @9RPM±SE) F1, Combined / 0 (20) / 273.8(±1.5) 1.5 (20) / 270.9(±1.1) 3 (20) / 271.5(±1.3) 4.5 (20) / 270.8(±2.5) no statistically significant effect on muscular grip strength

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental	
Reference and Dosing Protocol	**Results by Endpoint**
	observed up to 4.5 mg/kg
	open field activity
	Generation, Sex F1, Combined no statistically significant effect on head elevation, hind limb elevation, rearing, fecal boluses, urination, grooming, sniffing, biting and licking, head bobbing, auditory startle, pivoting, or gait abnormality observed up to 4.5 mg/kg
	palmar grasp observed
	Generation, Sex / Dose(n) / Response (PND±SE) F1, Combined / 0 (20) / 17.6(±0.25) 1.5 (20) / 17.44(±0.28) 3 (20) / 17.36(±0.9) 4.5 (20) / 17.5(±0.6) no statistically significant effect on palmar grasp observed up to 4.5 mg/kg
	startle reflex observed
	Generation, Sex / Dose(n) / Response (PND±SE) F1, Combined / 0 (20) / 25.08(±0.33) 1.5 (20) / 24.96(±0.37) 3 (20) / 25.12(±0.37) 4.5 (20) / 25.04(±0.35) no statistically significant effect on startle reflex observed up to 4.5 mg/kg
	surface righting reflex
	Generation, Sex F1, Combined no statistically significant effect on surface righting reflex observed up to 4.5 mg/kg
	T-maze
	Generation, Sex / Dose(n) / Response (%) F1, Combined / 0 (20) / 100 1.5 (20) / 99.91 3 (20) / 99.54 4.5 (20) / 99.56 no statistically significant effect on spontaneous activity in the T-maze evaluation up to 4.5 mg/kg
	tail pinch observed
	Generation, Sex / Dose(n) / Response (PND±SE) F1, Combined / 0 (20) / 23.64(±0.92) 1.5 (20) / 22.92(±1.37) 3 (20) / 23.48(±0.23) 4.5 (20) / 23.72(±0.8) no statistically significant effect on tail pinch observed up to 4.5 mg/kg
(Markowski et al., 2012)	**aberrant behaviors (shudder/spasm, intense grooming,**

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental	
Reference and Dosing Protocol	**Results by Endpoint**
Dosing Design: reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, C57BL/6J **Route of Exposure:** oral - water **Administered Doses:** F1, combined (NR): 0, 8, 25, 80 ppm; F1, female (NR): 0, 8, 25, 80 ppm; F1, male (NR): 0, 8, 25, 80 ppm **Dosing Description:** P0 dams exposed GD4 through GD18 or PND0 (whichever came first)	**dorsoflexion)** Generation, Sex F1, Combined all treated groups had a higher incidence of aberrant behaviors from PND17-21
	false alarm response Generation, Sex F1, Combined significant increase in the false alarm rate in the 8 ppm animals during the first 4 sessions
	grip strength Generation, Sex F1, Female all treated groups had a significant decrease in grip strength
	Generation, Sex F1, Male all treated groups had a significant decrease in grip strength
	intertrial interval response Generation, Sex F1, Combined significant decrease in all treated groups from session 12 to 24
	lever run rate Generation, Sex F1, Combined arsenic impacted lever run rate with higher-order sex-by-RR-by-session-by-exposure interaction [P=0.03] and earned food [P=0.01]
	locomotor counts Generation, Sex F1, Combined no statistically significant effect on locomotor counts observed up to 80 ppm at 2 months or puberty
	response rate Generation, Sex F1, Combined arsenic impacted response rate with sex-by-session-by-exposure interaction [P=0.03]
	righting reflex Generation, Sex F1, Combined significant decrease in righting reflex in all treatment groups
	spontaneous activity Generation, Sex F1, Combined all treated groups had significantly less spontaneous

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental	
Reference and Dosing Protocol	**Results by Endpoint**
	activity
	startle response
	Generation, Sex F1, Combined all treated groups had a significantly reduced acoustic startle on PND 13
(Martinez et al., 2008) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenate - Na2HAsO4 **Species and Strain:** mice, C57BL/6J **Route of Exposure:** oral - water **Administered Doses:** F1, combined (NR): 0, 0.05 ppm; F1, female (NR): 0, 0.05 ppm; F1, male (NR): 0, 0.05 ppm **Dosing Description:** P0 dams exposed daily 2 weeks before breeding through weaning (PND23)	**forced swim task (total immobility times, secs)**
	Generation, Sex F1, Combined total immobility time was significantly increased in arsenic treated animals (0.05 ppm) compared to controls (p<0.001)
	latency to escape
	Generation, Sex F1, Female perinatal arsenic (0.05 ppm) caused a significant increase in latency to escape in female offspring (p<0.0001)
	Generation, Sex F1, Male perinatal arsenic (0.05 ppm) caused a significant increase in latency to escape in male offspring (p<0.0001)
(Martinez-Finley et al., 2009) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenate - Na2HAsO4 **Species and Strain:** mice, C57BL/6J **Route of Exposure:** oral - water **Administered Doses:** F1, combined (NR): 0, 0.055 ppm **Dosing Description:** P0 males and females exposed daily for 2 weeks before breeding; dams continued treatment until weaning at PND23	**8-way radial arm maze**
	Generation, Sex F1, Combined significant effect of treatment (p<0.0001) in number of entry errors for arsenic exposed animals over 3 days of testing compared to controls at 0.055 ppm
	novel object exploration
	Generation, Sex F1, Combined latency to approach novel object after acclimation period was significantly slower (p<0.0001) in treated versus control animals; number of entries to center in presence of the novel object was significantly lower than control (p<0.0006) at 0.055 ppm
	whole brain weight; hippocampal wet weight
	Generation, Sex F1, Combined no statistically significant effect on whole brain weight or hippocampal wet weight observed at 0.055 ppm
(Ramsey et al., 2013c) **Dosing Design:** reproductive/developmental **Chemical:** Sodium Arsenite - NaAsO2 **Species and Strain:** mice, C57BL/6 **Route of Exposure:** oral - water **Administered Doses:** F1, combined (NR): 0, 10, 100 µg/L **Dosing Description:** P0 dams treated daily from GD8 through PND0	**birth length**
	Generation, Sex: F1, Combined Dose(n): 0 (NR); 10 (NR); 100 (NR) Response (mm±SD): 29.1(±1.74); 28.8(±1.94); 28.4(±1.9)* significantly lower birth length in fetal mice at 100 ug As/L (p <0.001) but not 10 ug As/L compared to control (p >0.47)

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental	
Reference and Dosing Protocol	**Results by Endpoint**
	birth weight Generation, Sex / Dose(n) / Response (g±SD) F1, Combined / 0 (NR) / 1.34(±0.16) 10 (NR) / 1.35(±0.19) 100 (NR) / 1.27(±0.18)* significantly lower birth weight in fetal mice exposed to 100 ug As/L in utero compared to control (p <0.001), but no significant difference in birth weight in fetal mice exposed to 10 ug As/L compared to control (p >0.47)
(Rodríguez et al., 2002) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** rat, Sprague-Dawley **Route of Exposure:** oral - water **Administered Doses:** F1, combined (29-32/group): 0, 36.7 mg/L; F1, male (13-15/group): 0, 0, 36.7, 36.7 mg/L **Dosing Description:** P0 dams exposed daily from PND1 until weaning; F1 males dosed daily through PND91 (F1 females not directly dosed)	**body weight of pups** Generation, Sex / Dose(n) / Response (g±SE) F1, Combined / 0 (11-12) / 290.49(±18.34) 36.7 (10-11) / 261.7(±18.33)* body weight significantly reduced beginning at 4 weeks and continuing until week 17 at 36.7 mg/L
	eye opening Generation, Sex F1, Combined no statistically significant effect on eye opening observed at 36.7 mg/L
	learning tasks - delayed alternation Generation, Sex F1, Male significantly increased mean number of errors at 36.7 mg/L (p<0.05) but no significant effect on latency
	learning tasks - spontaneous alternation Generation, Sex F1, Male no statistically significant effect on spontaneous alternation observed at 36.7 mg/L
	motor coordination Generation, Sex F1, Male no statistically significant effect on motor coordination observed at 36.7 mg/L
	onset of reflexes: righting reflex, negative geotaxis, pivoting, mid-air righting reflex, forelimb grip strength Generation, Sex F1, Combined no statistically significant effect on onset of reflexes including righting reflex, negative geotaxis, pivoting, mid-air righting reflex, and forelimb grip strength observed at 36.7 mg/L
	pinna detachment Generation, Sex F1, Combined no statistically significant effect on pinna detachment observed at 36.7 mg/L
	spontaneous locomotor activity: total distance, vertical

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental	
Reference and Dosing Protocol	**Results by Endpoint**
	activity, horizontal activity, vertical movements Generation, Sex F1, Male no statistically significant effect on locomotor variables at 13 or 17 weeks at 36.7 mg/L
(Rodríguez et al., 2002) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** rat, Sprague-Dawley **Route of Exposure:** oral - water **Administered Doses:** F1, combined (22-32/group): 0, 36.7 mg/L; F1, male (11-15/group): 0, 36.7 mg/L **Dosing Description:** P0 dams exposed daily from GD15 until weaning; F1 males exposed from weaning until 13 wks of life (F1 females not directly dosed)	**eye opening** Generation, Sex F1, Combined significantly lower eye opening scores observed at 36.7 mg/L on PND 14 (p<0.05) on PND 14
	learning tasks - delayed alternation Generation, Sex F1, Male significantly increased mean number of errors observed at 36.7 mg/L (p<0.05); no significant effect on latency
	learning tasks - spontaneous alternation Generation, Sex F1, Male no statistically significant effect on spontaneous alternation observed at 36.7 mg/L
	mean body weight of pups Generation, Sex: F1, Combined Dose(n): 0 (11-12); 36.7 (10-11) Response (g±SE): 290.49(±18.34); 276.02(±18.35)* significantly reduced overall at 36.7mg/L but no significant differences were observed at individual observation times
	motor coordination Generation, Sex F1, Male no statistically significant effect on motor coordination observed at 36.7 mg/L
	onset of reflexes: righting reflex, negative geotaxis, pivoting, mid-air righting reflex, forelimb grip strength Generation, Sex F1, Combined no statistically significant effect on the onset of reflexes observed at 36.7 mg/L
	pinna detachment Generation, Sex F1, Combined significantly more litters showed full pinna detachment at 36.7 mg/L on PND 12 (p<0.05)
	spontaneous locomotor activity: total distance, vertical activity, horizontal activity, vertical movements Generation, Sex F1, Male significantly increased vertical activity and vertical movements at both 13 and 17 weeks at 36.7 mg/L (p<0.05); no significant differences in total distance or

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental			
Reference and Dosing Protocol	**Results by Endpoint**		
	horizontal activity variables		
(Xi et al., 2009) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** rat, Wistar **Route of Exposure:** oral - water **Administered Doses:** F1, combined (12/group): 0, 10, 50, 100 mg/L **Dosing Description:** P0 dams treated daily GD6 through PND42; F1 treated daily PND28 through PND42	**air righting**		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	80.33
		10 (69)	92.54*
		50 (58)	73.21
		100 (58)	68.63
	auditory startle		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	98.44
		10 (69)	97.06
		50 (58)	100
		100 (58)	84.31*
	avoidance test: learning session: latency of reaction		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	157.25(±107.93)
		10 (12)	173.92(±132.58)
		50 (12)	127.5(±129.04)
		100 (12)	116(±136.02)
	avoidance test: long memory session: latency of reaction		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	166.67(±46.19)
		10 (12)	139.58(±73.19)
		50 (12)	98.83(±85.04)*
		100 (12)	125.08(±81.14)
	avoidance test: short memory session: latency of reaction		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	136.25(±65.2)
		10 (12)	129.08(±75.76)
		50 (12)	115.83(±80.25)
		100 (12)	117.5(±79.21)
	cliff avoidance		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	55.1
		10 (69)	68.97
		50 (58)	51.79
		100 (58)	56.6
	forelimb hung		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	93.75
		10 (69)	97.01
		50 (58)	98.25
		100 (58)	100
	negative geotaxis		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	71.93

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental			
Reference and Dosing Protocol	**Results by Endpoint**		
		10 (69)	69.23
		50 (58)	84.21
		100 (58)	63.04
	postnatal body weight		
	Generation, Sex		
	F1, Combined		
	body weight significantly decreased in 10, 50, and 100 mg/L arsenic-treated groups at PND 42, 16, and 12, respectively ($p<0.05$)		
	rotarod test: remain time		
	Generation, Sex		
	F1, Combined		
	no statistically significant effect on remain time on the bar (at 9 and 18 rpm) observed up to 100 mg/L		
	square water maze: learning session: latency		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	13(±4.81)
		10 (12)	14.08(±6.42)
		50 (12)	16.58(±8.72)
		100 (12)	20.17(±11.46)
	square water maze: learning session: trained number		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	6.67(±1.61)
		10 (12)	8.67(±2.15)
		50 (12)	10.08(±3.12)*
		100 (12)	11.67(±2.9)*
	square water maze: memory session: latency		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	12.08(±3.5)
		10 (12)	11.75(±4.09)
		50 (12)	14.33(±6.47)
		100 (12)	13.08(±5.18)
	square water maze: memory session: trained number		
	Generation, Sex	Dose(n)	Response (seconds±SE)
	F1, Combined	0 (12)	5.5(±1.83)
		10 (12)	6.92(±2.11)
		50 (12)	8(±2.92)
		100 (12)	8.08(±3.45)
	tail hung		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	89.06
		10 (69)	92.65
		50 (58)	93.1
		100 (58)	70.77*
	tail pinch		

Summary of Toxicology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental			
Reference and Dosing Protocol	**Results by Endpoint**		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	100
		10 (69)	100
		50 (58)	100
		100 (58)	98.18
	visual placing		
	Generation, Sex	Dose(n)	Response (%)
	F1, Combined	0 (64)	83.33
		10 (69)	68.85
		50 (58)	84.62
		100 (58)	60.87*

7.1.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Developmental Effects including Neurodevelopmental

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7.2 Summary of Observational Animal Studies for Health Effect Category: Immune System and Lymphatic Effects

Summary of Toxicology Studies for Health Effect Category: Immune System and Lymphatic Effects			
Reference and Dosing Protocol	**Results by Endpoint**		
(Das et al., 2012b) **Dosing Design:** chronic (>90 days) **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** goat, not reported **Route of Exposure:** oral - capsule **Administered Doses:** female (6/group): 0, 50 mg/kg **Dosing Description:** administered daily for 1 year	**lymphocyte stimulation index (SI)**		
	Sex	Dose(n)	Response (unitless±SE)
	Female	0 (6)	1.286(±0.03)
		50 (6)	1.003(±0.01)*
	significantly lower SI from 270 days onward		
	plasma total Ig concentration		
	Sex	Dose(n)	Response (mg/mL±SE)
	Female	0 (6)	22.28(±0.83)
		50 (6)	17.61(±0.78)*
	significantly increased total Ig at 4 months; significant declining trend at 9-12 months		
(Kozul et al., 2009) **Dosing Design:** subchronic (30 days to <90 days) **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, C57BL/6J **Route of Exposure:** oral - water **Administered Doses:** male (NR): 0, 100 ppb **Dosing Description:** animals (6-8/group) treated for 5 weeks followed by intranasal inoculation with sublethal dose of influenza virus	**altered cellular numbers in BALF**		
	Sex		
	Male		
	at day 7 post-infection, 100-ppb arsenic-exposed mice had significant increase in number of cells, neutrophils, and macrophages in BALF (p <0.001; Figure 4A)		
	dendritic cells migration capacity		
	Sex		
	Male		
	significant decrease for mice exposed at 100 ppb in migration capability toward ADP in transwell assay (p <0.001; Figure 7D)		
	total dendritic cells recovered in mediastinal lymph nodes		
	Sex		
	Male		
	decrease in number of dendritic cells in mediastinal lymph nodes of 100-ppb exposed mice early in the course of infection (day 3 post-infection) (p <0.01; Figure 7A)		
	viral titers		
	Sex		
	Male		
	arsenic exposure at 100 ppb significantly increased viral titers on day 7 post-infection (p <0.05; Figure 2)		
(Nain and Smits, 2012) **Dosing Design:** chronic (>90 days) **Chemical:** arsenite - As(OH)3 **Species and Strain:** rat, Wistar **Route of Exposure:** oral - water **Administered Doses:** male (6/group): 0, 0.4, 4, 40 ppm	**antibody-mediated IgG in plasma**		
	Sex	Dose(n)	Response (µg/mL±SE)
	Male	0 (6)	981(±144.7)
		0.4 (6)	-
		4 (6)	625(±104.6)*
		40 (6)	396(±123.4)*

Summary of Toxicology Studies for Health Effect Category: Immune System and Lymphatic Effects			
Reference and Dosing Protocol	**Results by Endpoint**		
Dosing Description: ad libitum for 18 weeks	**antibody-mediated IgM in plasma**		
	Sex	Dose(n)	Response (µg/mL±SE)
	Male	0 (6)	140(±5.9)
		0.4 (6)	-
		4 (6)	122(±13.8)
		40 (6)	130(±25.2)
	chemiluminescence		
	Sex	Dose(n)	Response (absorbance±SE)
	Male	0 (6)	2853(±39.4)
		0.4 (6)	-
		4 (6)	3756(±413.9)
		40 (6)	3275(±37.5)
(Ramsey et al., 2013b) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, C57BL/6 **Route of Exposure:** oral - water **Administered Doses:** F1, combined (NR): 0, 100 µg/L **Dosing Description:** dams exposed GD8 through weaning; offspring exposed until PND49	**BALF: total cells, neutrophils, macrophages, and lymphocytes**		
	Generation, Sex F1, Combined significant effect of arsenic exposure at 3 days but not at later time points up to 7 weeks for total cells and number of macrophages in BALF; no other compound-related effects for BALF parameters		
	IL-6, IFN-gamma, TNF-alpha, MCP-1, protein, viral titer		
	Generation, Sex F1, Combined no statistically significant effect observed on viral titer at 100 µg/L		
(Ramsey et al., 2013b) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, C57BL/6 **Route of Exposure:** oral - water **Administered Doses:** F1, combined (NR): 0, 100 µg/L **Dosing Description:** dams exposed GD8 through weaning; offspring (infected with influenza at 1 week) exposed until PND49	**BALF: total cells, neutrophils, macrophages, and lymphocytes**		
	Generation, Sex F1, Combined significant effect of arsenic in flu-infected animals for total cells in BALF and macrophages at 3 days post infection; significant interaction between arsenic exposure and flu treatment for total cells at 7 days post infection and for neutrophils at 7 days post infection		
	IL-6, IFN-gamma, TNF-alpha, MCP-1, protein, viral titer		
	Generation, Sex F1, Combined significant effect of arsenic exposure in flu-infected animals for viral titer at 7 days post infection only		
(Sankar et al., 2013) **Dosing Design:** subchronic (30 days to <90 days) **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** rat, Wistar **Route of Exposure:** oral - water **Administered Doses:** male (6/group): 0, 25 ppm **Dosing Description:** ad libitum for 42 days	**delayed-type hypersensitivity response (% increase in skin thickness)**		
	Generation, Sex	Dose(n)	Response (%±SE)
	Male	0 (6)	45(±3.41)
		25 (6)	24.17(±3.27)*
	secondary antibody production		
	Generation, Sex	Dose(n)	Response
	Male	0 (6)	0.731(±0.02)
		25 (6)	0.498(±0.01)*

Summary of Toxicology Studies for Health Effect Category: Immune System and Lymphatic Effects	
Reference and Dosing Protocol	**Results by Endpoint**
	T cell stimulation index Generation, Sex / Dose(n) / Response (unitless±SE) Male / 0 (6) / 0.559(±0.04) 25 (6) / 0.327(±0.03)* significantly decreased splenocyte lymphocyte proliferation as evidenced by decreased stimulation index
(Stępnik et al., 2009) **Dosing Design:** chronic (>90 days) **Chemical:** sodium arsenate - Na2HAsO4 **Species and Strain:** mice, C57BL/6J/Han **Route of Exposure:** oral - water **Administered Doses:** female (100/group): 0, 50, 200, 500 µg/L **Dosing Description:** animals on normal selenium diet (low-selenium diet also evaluated) dosed daily for 24 months	**malignant lymphoma** Sex / Dose(n) / Response (incidence) Female / 0 (83) / 6/83 50 (90) / 10/90 200 (85) / 13/85 500 (90) / 22/90* malignant lymphoma showed clear arsenic concentration-dependent increase of incidence; results similar for animals fed a low-selenium diet
	thymus, lymph node, spleen Sex Female no significant association between lesion type and arsenic exposure (up to 500 µg/L) or selenium status
(Waalkes et al., 2006b) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, CD-1 **Route of Exposure:** oral - water **Administered Doses:** F1, female (35/group): 0, 85 ppm **Dosing Description:** P0 dams exposed daily GD8 through GD18	**lymphoma** Generation, Sex / Dose(n) / Response (incidence) F1, Female / 0 (33) / 10/33 85 (34) / 2/34*

7.2.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: : Immune System and Lymphatic Effects

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7.3 Summary of Observational Animal Studies for Health Effect Category: Liver Effects

Summary of Toxicology Studies for Health Effect Category: Liver Effects			
Reference and Dosing Protocol	**Results by Endpoint**		
(Nain and Smits, 2012) **Dosing Design:** chronic (>90 days) **Chemical:** arsenite - As(OH)3 **Species and Strain:** rat, Wistar **Route of Exposure:** oral - water **Administered Doses:** male (6/group): 0, 0.4, 4, 40 ppm **Dosing Description:** ad libitum for 18 weeks	**liver histopathology (degree of vacuolization)**		
	Sex	Dose(n)	Response (grade±SE)
	Male	0 (6)	1.7(±0.21)
		0.4 (6)	2(±0.58)*
		4 (6)	2.8(±0.17)*
		40 (6)	3.2(±0.31)*
(Stępnik et al., 2009) **Dosing Design:** chronic (>90 days) **Chemical:** sodium arsenate - Na2HAsO4 **Species and Strain:** mice, C57BL/6J/Han **Route of Exposure:** oral - water **Administered Doses:** female (100/group): 0, 50, 200, 500 µg/L **Dosing Description:** animals on normal selenium diet (low-selenium diet also evaluated) dosed daily for 24 months	**liver adenoma or haemangioma**		
	Sex	Dose(n)	Response (incidence)
	Female	0 (83)	0/83
		50 (90)	2/90
		200 (85)	1/85
		500 (90)	3/90
	liver focal nodular hyperplasia		
	Sex	Dose(n)	Response (incidence)
	Female	0 (83)	7/83
		50 (90)	5/90
		200 (85)	6/85
		500 (90)	6/90
	not significant in normal selenium group; for low-selenium group, significant increase in focal nodular hyperplasia at 50 µg/L		
(Tokar et al., 2011) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, CD-1 **Route of Exposure:** oral - water **Administered Doses:** F1, female (30/group): 0, 6, 12, 24 ppm; F1, male (30/group): 0, 6, 12, 24 ppm **Dosing Description:** P0 breeding pairs exposed daily 2 weeks prior to breeding; dams continued exposure through gestation and lactation and F1 offspring continued on treatment until 2 years of age	**liver adenoma**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (29)	1/29
		6 (29)	1/29
		12 (28)	2/28
		24 (28)	1/28
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (29)	2/29
		6 (29)	3/29
		12 (28)	3/28
		24 (28)	6/28
	not significant		
	liver carcinoma		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (29)	0/29
		6 (29)	2/29
		12 (28)	2/28
		24 (28)	5/28*

Summary of Toxicology Studies for Health Effect Category: Liver Effects			
Reference and Dosing Protocol	**Results by Endpoint**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (29)	0/29
		6 (29)	4/29
		12 (28)	6/28*
		24 (28)	6/28*
	liver total adenoma and carcinoma		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (29)	1/29
		6 (29)	3/29
		12 (28)	4/28
		24 (28)	6/28*
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (29)	2/29
		6 (29)	6/29
		12 (28)	7/28
		24 (28)	10/28*
(Tokar et al., 2012) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, CD-1 **Route of Exposure:** oral - water **Administered Doses:** F1, male (50/group): 0, 85 ppm **Dosing Description:** P0 dams exposed daily from GD8 through GD18	**hepatic adenoma**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (49)	5/49
		85 (45)	5/45
	not significant		
	hepatic total tumors		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (49)	8/49
		85 (45)	14/45
	not significant; arsenic+DMA group significantly increased compared with control, arsenic-only, and DMA-only groups		
	hepatocellular carcinoma		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (49)	3/49
		85 (45)	9/45*
	also significantly increased incidence for arsenic+DMA group compared with control, DMA-only, and arsenic-only groups		
(Waalkes et al., 2004b) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, C3H **Route of Exposure:** oral - water **Administered Doses:** F1, female (25/group): 0, 42.5, 85 ppm; F1, male (25/group): 0, 42.5, 85 ppm **Dosing Description:** P0 dams exposed daily from GD8 through GD18	**hepatocellular adenoma**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (24)	2/24
		42.5 (23)	3/23
		85 (21)	3/21
	not significant; similar results in animals treated with TPA		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (24)	10/24

Summary of Toxicology Studies for Health Effect Category: Liver Effects	
Reference and Dosing Protocol	**Results by Endpoint**
	42.5 (23) 12/23 85 (21) 19/21* significant at 85 ppm; results similar for animals treated with TPA
	hepatocellular carcinoma
	Generation, Sex / Dose(n) / Response (incidence) F1, Female / 0 (24) / 1/24 42.5 (23) / 3/23 85 (21) / 1/21 not significant; similar results in animals treated with TPA
	Generation, Sex / Dose(n) / Response (incidence) F1, Male / 0 (24) / 3/24 42.5 (23) / 8/23 85 (21) / 10/21* significant at 85 ppm; results similar for animals treated with TPA
	hepatocellular tumors: multiplicity
	Generation, Sex / Dose(n) / Response (no./animal±SE) F1, Female / 0 (24) / 0.13(±0.07) 42.5 (23) / 0.41(±0.16) 85 (21) / 0.29(±0.14) not significant; in animals treated with TPA, significant increase in multiplicity at 85 ppm
	Generation, Sex / Dose(n) / Response (no./animal±SE) F1, Male / 0 (24) / 0.75(±0.16) 42.5 (23) / 1.87(±0.45)* 85 (21) / 2.14(±0.27)* significant increase at ≥ 42.5 ppm; results similar for animals treated with TPA
	hepatocellular tumors: total
	Generation, Sex / Dose(n) / Response (incidence) F1, Female / 0 (24) / 3/24 42.5 (23) / 6/23 85 (21) / 4/21 not significant; in animals treated with TPA, significant increase in total tumor incidence at 85 ppm
	Generation, Sex / Dose(n) / Response (incidence) F1, Male / 0 (24) / 12/24 42.5 (23) / 14/23 85 (21) / 19/21* significant increase at 85 ppm; results similar for animals treated with TPA
(Waalkes et al., 2006a) **Dosing Design:** reproductive/developmental	**liver adenoma** Generation, Sex / Dose(n) / Response

Summary of Toxicology Studies for Health Effect Category: Liver Effects			
Reference and Dosing Protocol	**Results by Endpoint**		
Chemical: sodium arsenite - NaAsO2 **Species and Strain:** mice, CD-1 **Route of Exposure:** oral - water **Administered Doses:** F1, male (35/group): 0, 85 ppm **Dosing Description:** P0 dams exposed daily from GD8 through GD18			(incidence)
	F1, Male	0 (35)	2/35
		85 (35)	8/35*
	liver carcinoma		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (35)	0/35
		85 (35)	5/35*
	liver total tumors		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (35)	2/35
		85 (35)	11/35*
(Waalkes et al., 2006b) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, CD-1 **Route of Exposure:** oral - water **Administered Doses:** F1, female (35/group): 0, 85 ppm **Dosing Description:** P0 dams exposed daily GD8 through GD18	**liver: total mesenchymal and epithelial tumors**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (33)	0/33
		85 (34)	4/34
(Waalkes et al., 2003) **Dosing Design:** reproductive/developmental **Chemical:** sodium arsenite - NaAsO2 **Species and Strain:** mice, C3H **Route of Exposure:** oral - water **Administered Doses:** F1, female (23-25/group): 0, 42.5, 85 ppm; F1, male (21-24/group): 0, 42.5, 85 ppm **Dosing Description:** P0 dams exposed daily from GD8 through GD18	**liver adenoma**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (24)	7/24
		42.5 (21)	3/21
		85 (23)	6/23
	adenoma and carcinoma observed in some animals resulting in a significantly increased nominal rate of adenoma incidence ($p<0.001$) at the high-dose level		
	liver adenoma multiplicity (tumors/mouse)		
	Generation, Sex	Dose(n)	Response (#/mouse±SE)
	F1, Male	0 (24)	0.71(±0.22)
		42.5 (21)	1.43(±0.49)
		85 (23)	3.61(±0.78)*
	liver carcinoma		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (24)	3/24
		42.5 (21)	8/21*
		85 (23)	14/23*
	liver carcinoma multiplicity (tumors/mouse)		
	Generation, Sex	Dose(n)	Response (#/mouse±SE)
	F1, Male	0 (24)	0.13(±0.07)
		42.5 (21)	0.42(±0.13)
		85 (23)	1.3(±0.28)*
	liver histological analysis: adenoma		

Summary of Toxicology Studies for Health Effect Category: Liver Effects			
Reference and Dosing Protocol	**Results by Endpoint**		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (25)	5/25
		42.5 (23)	3/23
		85 (24)	3/24
	liver tumor incidence and multiplicity unaltered by arsenic exposure		
	liver histological analysis: carcinoma		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Female	0 (25)	0/25
		42.5 (23)	1/23
		85 (24)	1/24
	liver tumor incidence and multiplicity unaltered by arsenic exposure		
	liver total tumor multiplicity (tumors/mouse)		
	Generation, Sex	Dose(n)	Response (#/mouse±SE)
	F1, Male	0 (24)	0.87(±0.25)
		42.5 (21)	1.81(±0.54)
		85 (23)	4.91(±0.92)*
	liver total tumors		
	Generation, Sex	Dose(n)	Response (incidence)
	F1, Male	0 (24)	10/24
		42.5 (21)	11/21
		85 (23)	20/23*

7.3.1 References for Summary of Observational Epidemiology Studies for Health Effect Category: Liver Effects

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8 MODE OF ACTION (MOA) LITERATURE SEARCH STRATEGY FOR THE TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC

8.1 Overview of Literature Search Strategy

The mode of action literature search strategy began with all references from initial arsenic literature search that were not found in the health effects cluster (see Figure 3.1-1). References from the health effects cluster had already been reviewed and references discussing mode of action identified. The identified mode of action references from the health effect cluster will be considered during evaluation of the mode of action literature.

For references not found in the health effects cluster (~24,000), a combination of automated and manual selection process was used to identify relevant mode of action literature. OmniViz reference visualization software was used to form clusters of references using natural language processing. Natural language processing groups references based on language similarity in the title and abstract. To identify references relevant for mode of action, approximately 400 references were used as "seed" references. "Seed" references are those previously identified by experts as relevant to mode of action in peer reviewed inorganic arsenic human health risk assessments. Clusters containing many seed items have a higher probability of relevance to the topics discussed by the references in the seed. Those clusters with a smaller number of seeds have a decreasing probability, and those with none have a low probability of relevance. All the clusters that contain at least one seed reference were reviewed. While this approach does not specifically identify individual references, it does identify groups of references that have a higher probability of relevance.

The subset of mode of action clusters will be considered, along with references identified from the original health effects cluster.

9 INORGANIC ARSENIC MODE OF ACTION (MOA) HYPOTHESIS SUMMARIES

9.1 Preamble

9.1.1 Background

The series of tables and summaries that follow provide a foundation for a discussion with stakeholders attending a bimonthly meeting for the Integrated Risk Information System (IRIS). As described in the inorganic arsenic assessment development plan (ADP), EPA will use an adverse outcome pathway (AOP) framework to inform potential human health effects associated with inorganic arsenic exposures. Information in an AOP framework supports the use of mode of action (MOA) data as a basis for understanding adverse effects (OECD, 2013). AOP and MOA analyses support hazard identification and dose-response analysis decisions and are not in of themselves a requirement for organization of the available health effects information. Each summary and accompanying table below presents one of several hypothesized MOAs that may be relevant to understanding adverse health outcomes following inorganic arsenic exposures in human populations[1]. EPA defines the term MOA as "a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation [or other adverse outcomes]" (U.S. EPA, 2005). In instances when data are available to establish 1) the initial interaction between an agent and a cell (i.e., molecular initiating event), and 2) an adverse outcome relevant to risk assessment, then a MOA may be similar to an AOP (OECD, 2013; Ankley et al., 2010). In instances when data are not available to establish both of these anchors, then MOA may be used to organize data and identify data gaps. The MOA framework is used consistently throughout these discussion materials in anticipation of subsequently developing AOPs when sufficient data are available.

The hypothesized MOAs were selected based on available information from authoritative reports and reviews on inorganic arsenic MOA (Cohen et al., 2013; NRC, 2013; Jomova et al., 2011; Kitchin and Conolly, 2010; Prins, 2008). EPA understands that these MOAs are not exhaustive; discussions during the IRIS bimonthly meeting may help to identify

[1] Efforts to develop summaries and tables for hypothesized MOAs are ongoing; a subset of the MOA discussion materials is available in the current draft.

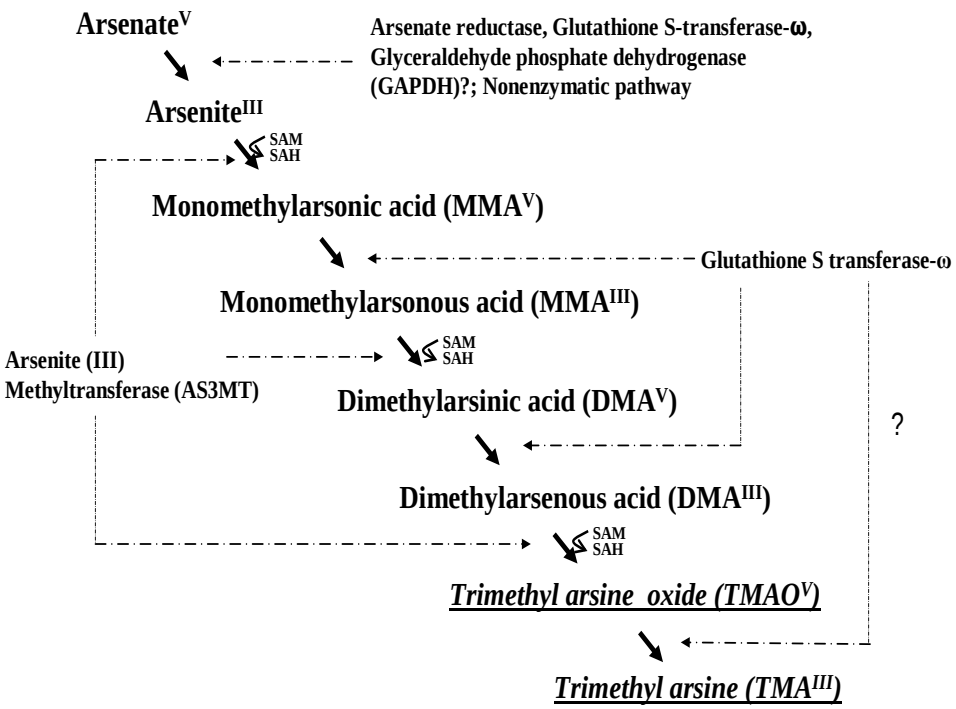
additional MOAs relevant for consideration in understanding adverse health effects of inorganic arsenic, and provide insight on interactions between multiple MOAs that could influence subsequent health effects. This approach anticipates that reviewers of these materials will also identify additional literature to inform evaluations of MOAs relevant to particular health outcomes in the IRIS assessment of inorganic arsenic. The following summaries are not intended to provide a comprehensive presentation of available information, or to present EPA's interpretation of the identified literature; rather these summaries outline information from the identified literature on the main elements (i.e., molecular initiating events, key events, adverse outcomes) in a set of potentially key MOAs as a foundation for further discussion. As these MOAs are refined, additional documentation will be added based on information provided by reviewers of these materials and the results of EPA's comprehensive literature search. More information on the use of MOA data in the subsequent inorganic arsenic IRIS assessment is available in the ADP.

9.1.2 Considerations relevant across all hypothesized MOAs

There are a number of cross cutting issues that need to be considered in the evaluation of the various hypothesized MOAs. These include the metabolism of inorganic arsenic, and co-toxic and interactive effects.

9.1.2.1 Inorganic arsenic Metabolism

The metabolism of inorganic arsenic (Figure 9-1) is relevant to all of the hypothesized MOAs discussed below. However, to reduce redundancy in the presentations, the MOA discussions will begin by identifying the specific metabolites (where known) that interact with specific cellular molecules (where known) in the ***molecular initiating events*** for the MOA. Specific metabolic pathways of inorganic arsenic will be discussed for each MOA only to the extent that they are relevant to the evaluation of the MOA, to the explanation or species differences in effects, or in the identification of potentially susceptible populations [IRIS Handbook, Guidelines for carcinogen risk assessment (U.S. EPA, 2005), and Inorganic Arsenic ADP].



Source: Modified from Sams et al. (2007).

Figure 9-1 Traditional metabolic pathway for inorganic arsenic in humans.

The reader may refer to recent reviews (Cohen et al., 2013; Jomova et al., 2011) for more detailed information related to inorganic arsenic metabolism. Key elements of mammalian inorganic arsenic metabolism that bear on internal exposures and dosimetry include the following set of interrelated reactions:

- Enzymatic or non-biological reductions of pentavalent arsenic species to As(III) and other trivalent metabolites;
- Oxidative methylation of trivalent species to pentavalent methylarsonic acid (MMA[V]) and dimethylarsinic acid (DMA[V])

In rodents and humans, the net result of this "cascade" is to convert the bulk of inorganic arsenic to methylated species through a series of redox reactions. As a result, internal exposures after ingestion of inorganic arsenic tend to consist of mixtures of inorganic arsenic and trivalent methylated species. The exact patterns of internal dose are species- and target-organ specific, and vary based on exposure levels and duration, genetic background. Other minor metabolites (substituted arsines and thiolated metabolites) may

also be formed under certain conditions, and are postulated to play a role in some aspects of toxicity (Pinyayev et al., 2011). As noted above, the specifics of metabolic pathways will be discussed only where investigators identify them as being important aspects of the MOA. For example, the redox cascade has been implicated in the depletion of cellular thiol compounds and in the generation of reactive oxygen species; thus, the implications of these reactions are briefly noted as part of the relevant MOAs.

9.1.2.2 Co-toxic and interactive effects

As noted above, co-toxic and interactive effects between inorganic arsenic and other chemicals or stressors are relevant to many of the MOA summaries that follow. Factors that may generally impact susceptibility to inorganic arsenic exposure are noted here in order to support a discussion on populations that may be at increased risk due to cumulative or synergistic effects of inorganic arsenic and other chemicals or stressors. These factors include: life stage, nutrition, genetics, sex, and pre-existing disease (NRC, 2013). In addition, smoking, alcohol consumption, and exposure to mixtures may also increase vulnerability to the effects of inorganic arsenic (NRC, 2013). Inorganic arsenic has also been found to interact with other metals, like cadmium (Huang et al., 2009a), and polycylic aromatic hydrocarbons (PAHs) (Fischer et al., 2005; Maier et al., 2002).

The potential interactions between inorganic arsenic exposure and smoking or other co-exposures on individual responses have been assessed in epidemiological studies (Table in Section 10.6). The synergistic interaction between smoking and inorganic arsenic has been found to be greater than additive for skin lesions observed in Bangladesh (Chen et al., 2006a). An interaction between smoking and bladder cancer was also observed in New Hampshire (Karagas et al., 2004). In addition, synergistic effects between fertilizer use and inorganic arsenic exposure in well water were observed for skin lesions in Bangladeshi men participating in the Health Effects of Arsenic Longitudinal Study (HEALS) reported (Melkonian et al., 2011). The HEALS study results further suggested that men in this cohort, exposed to the same level of inorganic arsenic, with a history of smoking and high fertilizer use may be more susceptible to skin lesions than those with no smoking history or fertilizer use. Diets low in folate and other B vitamins have also been associated with increased risks of skin lesions and hypertension (Pilsner et al., 2009; Chen et al., 2007b; Mitra et al., 2004).

As the assessment development process moves forward, a more systematic approach to integrating information on factors that may have co-toxic and interactive effects with

inorganic arsenic will be undertaken. Input on this topic from stakeholders attending the IRIS bimonthly meeting would thus useful for EPA.

9.2 Hypothesized MOA: Cytotoxicity and Regenerative Proliferation

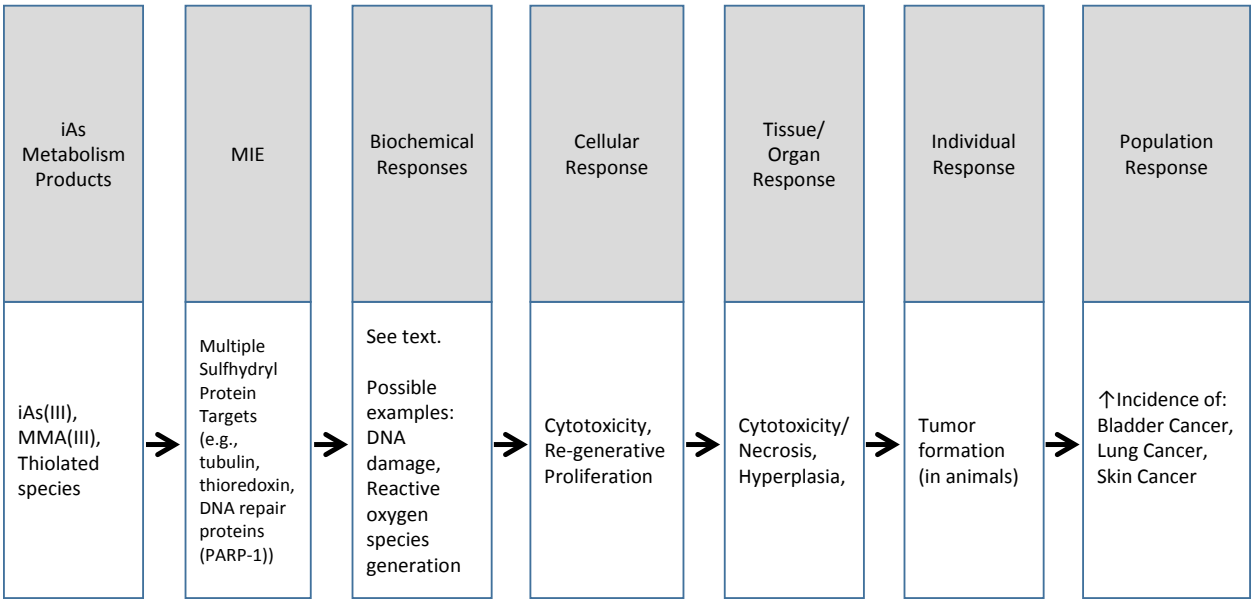
Relevant Health Effects: Bladder cancer, lung cancer, skin cancer

Cohen et al. (2013) have argued that the carcinogenic action of inorganic arsenic in the bladder is due to a mode of action (MOA) that includes cytotoxicity to urothelial cells followed by regenerative proliferation leading eventually to urothelial carcinoma. Cohen et al. (2013) have further argued that this MOA may also apply to lung and skin cancers. Prior to the molecular initiating events in this MOA, it is assumed that inorganic arsenic will be transformed into active metabolites (see Preamble). Under this MOA, exposure of sensitive tissue to the most toxic arsenic species, As(III) and MMA(III), and possibly thiolated species, results in the following sequence of events (Figure 9-2):

- Reaction with sulfhydryl groups of specific proteins in the target tissue,
- Cytotoxicity caused by the reactive metabolites,
- Regenerative proliferation (including hyperplasia) in tissues (e.g., urothelium), and
- Development of tumors (Cohen et al., 2013)

Cohen et al. (2013) propose that, following ingestion and metabolism of relatively large amounts of inorganic arsenic, the ***molecular initiating event*** (MIE) under this MOA is the **reaction of arsenic species with protein thiol groups** in epithelial cells. A number of specific protein thiol targets have been identified, mostly by in vitro studies, including tubulin, keratin, estrogen receptor-α (ERα), thioredoxin reductase, DNA repair associated proteins including PARP-1, XPA, and XPD. In vitro studies with synthetic peptides also indicate that inorganic arsenic species can react specifically with zinc finger motifs in transcription factors and regulatory proteins (Wnek et al., 2011; Kitchin and Wallace, 2008; Qin et al., 2008; Kitchin and Wallace, 2005). The specific protein interactions responsible for the observed cytotoxicity and subsequent proliferation have not been identified, however (Cohen et al., 2013). Variations between species and tissue types in the reactivity of different arsenic species with specific proteins could influence subsequent biochemical responses; as noted above, this mode of action has been investigated primarily in urothelial tissues but Cohen et al. (2013) suggest that it may also apply to lung and skin cancers based on their evaluation of available in vitro, in vivo animal and epidemiology data. As such, differences related to arsenic species and tissue

may be factors of interest to consider in future research on this MOA in these or other tissues according to (Cohen et al., 2013).



Abbreviations: Inorganic arsenic (iAs); Molecular Initiating Event (MIE); monomethylarsenous (MMA[III]); Poly [ADP-ribose] polymerase 1 (PARP-1)

See Summary Text and Table for references; Figure based on Ankley et al. (2010).

Note: This Figure shows an overview of key events from the initial molecular interaction of arsenic species with sulfhydryl protein targets through a possible population level response. As the assessment development process moves forward additional evidence may provide better understanding of key events in the MOA and the level of evidence available to support connections between key events.

Figure 9-2 Hypothesized mode of action for cytotoxicity and regenerative proliferation.

As usually formulated by Cohen et al. (2013), the regenerative proliferation MOA is silent with regard to the ***biochemical responses*** (i.e., molecular or genetic mechanisms) underlying the progression from MIE to cytotoxicity and subsequent proliferation to carcinogenic transformation. While some studies suggest that the molecular or genetic mechanisms in this MOA may include DNA strand breaks, altered transcription factor or growth factor activity, and generation of reactive oxygen species (ROS) (Wnek et al., 2011; Wnek et al., 2009; Eblin et al., 2008; Eblin et al., 2006; Simeonova et al., 2002; Simeonova et al., 2000), other evidence from a short-term study suggests that mitigating oxidative stress does not prevent regenerative proliferation, which implies that ROS is not a necessary step in the MOA (Suzuki et al., 2009). Additional studies were not

identified to further support or refute other possible biochemical responses; however, Cohen et al. (2013) suggest that understanding underlying biochemical mechanisms (e.g., oxidative stress, epigenetic effects on DNA and histones), and the direct interaction of arsenic species with cellular signaling pathways is of limited relevance because the dose-response for the key ***cellular responses*** (cytotoxicity and proliferation) have been so well established.

The first proposed key cellular response that Cohen et al. (2013) identify in this MOA is epithelial cell **cytotoxicity**. Evidence of cytotoxicity comes from a wide range of *in vitro* and *in vivo* studies. *In vitro*, the cytotoxicity of arsenic species (i.e., arsenite, MMA(III), DMA(III), and thiol derivatives) has been demonstrated in a number of primary and immortalized mammalian cell lines (Table in Section 10.1) (Suzuki et al., 2010; Eblin et al., 2008; Bredfeldt et al., 2006; Sens et al., 2004; Drobna et al., 2003; Cohen, 2002; Styblo et al., 2000). Cytotoxicity, as measured by LC_{50} or IC_{50}, varies greatly depending on the arsenic species being evaluated and the cell lines employed. *In vitro* acute cytotoxicity is greatest for the trivalent species (LC/IC50 values in the range of approximately 1-20 μM for As[III], MMA[III], DMA[III]) and lower for the pentavalent analogues (LC/IC_{50}s on the order of 30-1500 μM). Acute cytotoxicity of trivalent arsenic appears similar in primary cell lines and immortalized (UROTSA) cells. Limited data on the thiol analogues such as DMMAT(V) suggest that its acute toxicity is similar to the trivalent arsenicals (LC_{50} = 1.4-5.5 μM in urothelial and bronchioepithelial cells, respectively).

Cytotoxicity and **cellular necrosis** has also been observed at the ***organ or tissue*** level *in vivo* in a number of studies where rats and mice were exposed to inorganic arsenic in diet and drinking water (Table in Section 10.1) (Arnold et al., 2013; Yokohira et al., 2011; Suzuki et al., 2010; Yokohira et al., 2010; Suzuki et al., 2008). Data suggest that female rats are more sensitive to cytotoxic effects of inorganic arsenic than male rats or either sex in mice (Suzuki et al., 2008). Exposure via drinking also appears to elicit greater effects on the bladder compared to dietary exposure in rats and mice (Suzuki et al., 2008). Evidence also indicates that cytotoxicity in As3mt knockout mice was generally similar to those seen in the wild type and occurred at similar exposure levels as for As(III); suggesting that methylation was not necessarily a key step in acute cytotoxicity, and that unmethylated As(III) therefore likely played a role in the observed cytotoxic effects (Yokohira et al., 2011, 2010). *In vitro* studies of different cell lines also support a lack of correlation between arsenic methylation capacity and cytotoxicity (Styblo et al., 2000). Finally, a 14-day study in F344 rats and WT and As3mt knockout C57BL/6 mice found increasing incidence of elevated cytotoxicity scores in the urothelium over time (Arnold

et al., 2013). In rats, one animal showed isolated foci of cytotoxicity in the urothelium after only six hours of exposure, while larger numbers of rats (seven of ten) showed elevated cytotoxicity scores by the end of the experiment (14 days). Cytotoxicity scores were also elevated in both the wild type and As3mt knockout mice beginning at approximately 3 days of exposures.

Cohen et al. (2013) propose that the next key event in this MOA is increased cellular **(regenerative) proliferation** *at the organ or tissue level*, which was observed in several of the cytotoxicity studies just discussed (Table in Section 10.1). Simeonova et al. (2000) observed urothelial hyperplasia and metaplasia in female C57BL/6 mice exposed to 0.01% sodium arsenite in drinking water for four weeks or longer. Hyperplasia was accompanied by a "cobblestone" appearance of the urothelium, but not by necrotic cytotoxicity. Simeonova et al. (2000) subsequently observed urothelial hyperplasia and occasional squamous metaplasia in mice exposed to 50 and 100 μg/L As(III) for eight weeks. Suzuki et al. (2008), reported simple urothelial hyperplasia occurring roughly in parallel with increased cytotoxicity scores in rats and mice exposed to arsenite in food at 50-400 ppm or drinking water at 100 ppm for up to ten weeks. Subsequent studies with female rats confirmed a dose-dependent increase in cytotoxicity and urothelial hyperplasia following dietary exposures of 50 or 100 ppm for approximately 3-5 weeks (Suzuki et al., 2010; Suzuki et al., 2009). Yokohira et al. (2010) also observed both urothelial cytotoxicity and hyperplasia in C57BL/6 mice after as few as six days of exposure to 150 ppm arsenite in diet or four weeks exposure to 25 ppm arsenite in drinking water. Simultaneous occurrence of cytotoxicity and hyperplasia was confirmed by SEM observations in one mouse exposed to 150 ppm in food. Arnold et al. (2013) also found the incidence of both urothelial cytotoxicity and "mild simple hyperplasia" increasing over time in female rats exposed to 100 ppm inorganic arsenic in water for 14 days. While the number of animals involved was limited, the slight lag (18 hrs) between the earliest detectable increase in cytotoxicity scores and the occurrence of hyperplasia supports the proposed MOA as requiring cytotoxicity as a precursor event to increased (regenerative) proliferation. The focus on low, non-cytotoxic concentrations in in vitro studies, and the use of transformed cell lines for evaluating indicators of proliferation (e.g., reduced doubling time) complicates further substantiating the sequential relationship of cytotoxicity and regenerative proliferation in this MOA (Bredfeldt et al., 2006; Sens et al., 2004).

Cohen et al. (2013) define the apical ***individual response*** in this MOA as the **development of tumors** subsequent to regenerative proliferation. A methylated metabolite, dimethylarsinic acid [DMA(V)], has been found to lead to tumor

development in rats but not mice (Arnold et al., 2006) and the incidence of urothelial hyperplasia was also elevated in exposed animals. In contrast to the results for DMA(V), inorganic arsenic has generally not been found to be carcinogenic in conventional rodent bioassays with adult animals (reviewed by Tokar et al., 2010a). Differences in outcomes between exposures to inorganic arsenic and DMA(V) may arise due to metabolism or distribution of the compound in rats, which may not be relevant to metabolism or distribution in humans (Cohen et al., 2013). As discussed below, higher incidences of tumors in human populations with high exposures to inorganic arsenic suggest that this MOA is relevant for understanding adverse health outcomes in humans, and emphasizes the importance of recent efforts to develop new rodent models of inorganic arsenic carcinogenicity (Cohen et al., 2013).

In contrast to data in adult animals, inorganic arsenic has been found to cause tumors in rodents after exposures beginning *in utero* (Table in Section 10.1) (Tokar et al., 2011; Waalkes et al., 2004b; Waalkes et al., 2003). Early life exposures in mice to inorganic arsenic in drinking water resulted in significantly increased incidences of tumors in multiple tissues (Table in Section 10.1) in male and female offspring (Tokar et al., 2011; Waalkes et al., 2004b; Waalkes et al., 2003). Dose-related increases in hyperplasia were also seen in several tissues, including the bladder, ovaries, and uterus of the females (Tokar et al., 2011).

Data from in utero exposure studies in animals that show an association between early life exposures to inorganic arsenic and subsequent tumor development suggest that developing children may be an important susceptible population for effects associated with this MOA. Based on findings by Suzuki et al. (2008), females may also have greater susceptibility to effects associated with this MOA, although no other data were identified to support this possibility. Other factors that might contribute to individual susceptibility related to this MOA may include exposures to other substances causing cytotoxicity in the bladder or other target organs. As discussed above, variations in arsenic methylating ability in rodents do not correlate in straightforward manner with cytotoxic responses in the bladder. On the other hand, Chen et al. (Chen et al. (2003b); Chen et al. (2003a)) report that increased urinary MMA/DMA levels may be associated with increased risk of skin and bladder cancer, respectively in heavily exposed human populations.

With regard to ***population responses***, Cohen et al. also suggest that the available epidemiological studies support the regenerative proliferative mechanism, in that increased arsenic-related cancer risk has only clearly been demonstrated in populations with exposure to relative high doses of inorganic arsenic (reviewed in Cohen et al., 2013) (Table in Section 10.1). This would be consistent with a situation where increased cancer

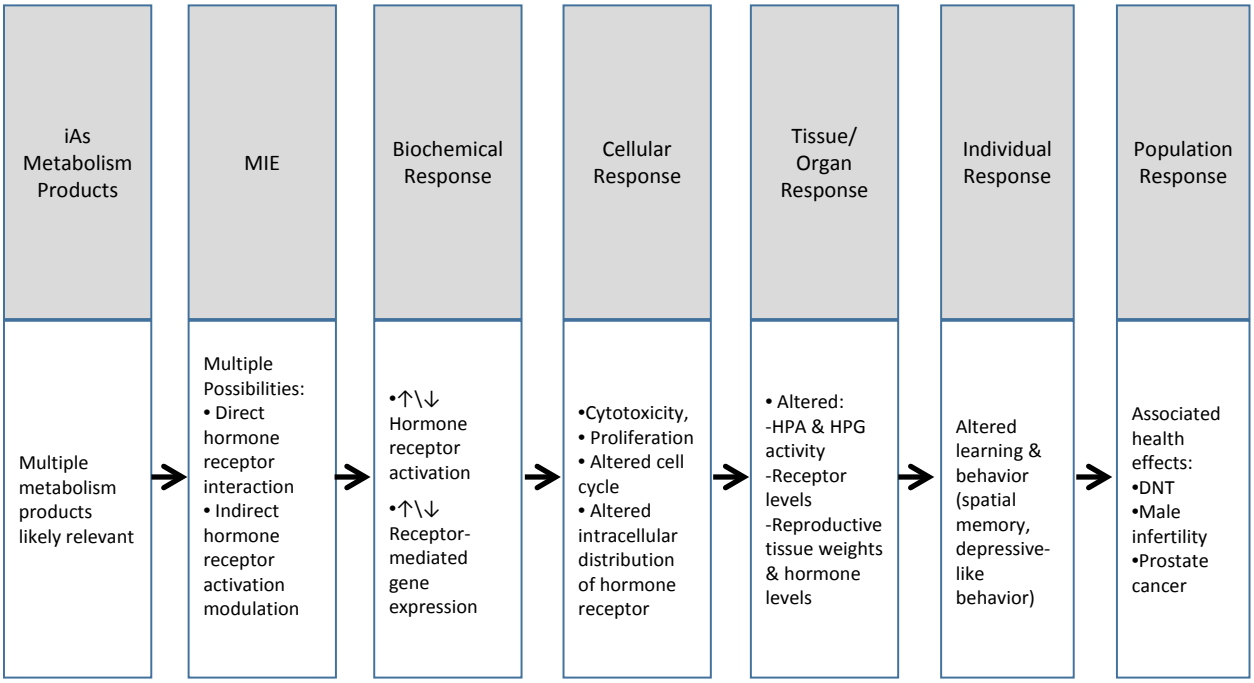
risk only occurred when internal concentrations of As(III) and/or other toxic metabolites reached levels associated with cytotoxicity, followed by regenerative proliferation and tumor development. However, very few epidemiological studies have been conducted with sufficient statistical power to detect small elevations in risk at low exposures and thus uncertainty is associated with the assertion of a threshold exposure below which elevated cancer risks do not occur. A full review of the epidemiological literature related to inorganic arsenic carcinogenicity is discussed separately in other documents prepared for the inorganic arsenic IRIS assessment.

9.3 Hypothesized MOA: Effects Mediated by Endocrine Signaling

Relevant Health Effects: Developmental Neurotoxicity, Male Infertility, Prostate Cancer

As discussed in the Preamble, inorganic arsenic metabolism leads to a number of metabolites; however, limited data were identified linking specific metabolites to the adverse health effects associated with the endocrine system. Nevertheless, several adverse health effects following exposure to inorganic arsenic may result from events mediated by the endocrine system (Goggin et al., 2012; Davey et al., 2008; Prins, 2008) (Figure 9-3). The ***molecular initiating event*** (MIE) in this MOA is a topic of ongoing research but based on literature reviewed for this summary may involve an interaction between inorganic arsenic and an element of the transcription complex for gene activation of nuclear hormone receptors. Specifically, inorganic arsenic may interact or modulate one of the following elements: 1) the hormone binding domain of the hormone receptor, 2) signaling pathways (e.g., mitogen activated protein kinases [MAPKs], extracellular signal-regulated kinases [ERK 1/2]) responsible for posttranslational modification of steroid hormone receptor proteins (e.g., coactivator phosphorylation), or 3) histone modifying proteins (i.e., acetylases, deacetylases, methylases) involved in receptor activation (Barr et al., 2009; Rosenblatt and Burnstein, 2009; Stoica et al., 2000). Notably, the first MIE option, interaction with the hormone binding domain, may be specific to estrogen receptor alpha (ERα), while the other possibilities may be more broadly applicable across both steroid receptors (e.g., glucocorticoid receptor [GR], progesterone receptor [PR], androgen receptor [AR], mineralocorticoids [MR]) and the larger class of nuclear hormone receptors (e.g., thyroid hormone receptor [TR], retinoic acid receptor [RAR]) (Davey et al., 2008; Bodwell et al., 2006; Stoica et al., 2000).

Across receptor types, the literature indicates that the MIE is followed by a series of ***biochemical responses*** that can be broadly characterized as altering **gene activation** and subsequent **cell signaling** mediated by nuclear hormone receptors (Table in Section 10.2). In the case of ERα, inorganic arsenic may alter gene activation by inhibiting binding of the natural ligand, estradiol (E2), to the receptor (Stoica et al., 2000). Low levels of inorganic arsenic (1 nM) can then activate the receptor at levels approaching that of E2 (Stoica et al., 2000). Activation of ERα results in altered expression of genes regulated by the receptor (e.g., vitellogenin, pS2, PR), which is measurable at the mRNA and protein levels (Davey et al., 2007; Stoica et al., 2000). Importantly, inorganic arsenic activation of ERα gene transcription is likely mediated by the receptor since treatment with antiestrogen blocks gene transcription mediated by the receptor (Stoica et al., 2000).



Abbreviations: Inorganic arsenic (iAs); molecular initiating events (MIEs); hypothalamic-pituitary-adrenal (HPA); hypothalamic-pituitary-gondal (HPG); developmental neurotoxicity (DNT)

See Summary Text and Table for references; Figure based on Ankley et al. (2010).

Note: Figure hows a high-level summary of key events from the initial molecular interaction through a possible population level response. The arrows link each key event (e.g., individual responses lead to population responses), but do not necessarily link each specific example response (e.g., behavioral changes are not linked to male infertility). Of particular note for this MOA is that evidence at the individual level was only identified for effects related to developmental neurotoxicity, even though population level responses indicate effects in other systems (i.e., reproductive effects). As the assessment development process moves forward additional evidence may provide better understanding of the key events in this MOA and the connections between them.

Figure 9-3 Hypothesized mode of action for effects mediated by endocrine signaling.

While the above sequence of biochemical responses is supported by one group of investigators, others provide evidence that responses at the ERα receptor are similar to those of other nuclear hormone receptors (e.g., GR, PR, TR, RAR) (Davey et al., 2007; Stoica et al., 2000). Under this second possible sequence of events, the MIE likely leads to alterations in posttranslational modifications (e.g., phosphorylation) of coactivator proteins (e.g., TIF2, GRIP1) that are critical for transcriptional activity at response elements for each receptor (e.g., glucocorticoid receptor response elements [GREs]) (Barr et al., 2009; Rosenblatt and Burnstein, 2009); these modifications may result in impaired interactions between coactivators (e.g., CARM1 and GRIP1) (Barr et al., 2009). Alternatively, the MIE may lead to alterations in histone modifications necessary for receptor-mediated gene activation (e.g., lower acetylation or methylation) (Barr et al., 2009). Ultimately, perturbations in the transcriptional complex impair receptor binding to response elements, leading to changes in receptor-mediated gene activation (Barr et al., 2009; Rosenblatt and Burnstein, 2009). Changes in gene activation mediated by inorganic arsenic through this MOA may result in either activation or suppression of gene activity. Where low levels of inorganic arsenic (i.e., nanomolar range) may elevate hormone-mediated gene activation, higher, non-cytotoxic concentrations may suppress hormone-mediated gene activation (Davey et al., 2008; Bodwell et al., 2006; Bodwell et al., 2004). In addition to different outcomes resulting from low versus higher inorganic arsenic exposure levels, differences in levels of hormone receptors may underlie different responses across organ and tissue types (Bodwell et al., 2006).

Differences in biochemical responses to inorganic arsenic may ultimately lead to changes in ***cellular responses*** (e.g., cell proliferation, cell death) that vary by cell type based on the factors noted above (e.g., receptor levels, ligand levels) (Rosenblatt and Burnstein, 2009; Davey et al., 2008; Davey et al., 2007; Stoica et al., 2000) (Table in Section 10.2). Data from three transformed cell lines show variation in the LC50 for cytotoxicity ranging from 3 to 15 µM (Davey et al., 2008; Davey et al., 2007). While most evidence suggests that cytotoxicity and proliferation elicited through this MOA are partially mediated by the natural hormone ligand (E2) (Rosenblatt and Burnstein, 2009; Davey et al., 2008; Davey et al., 2007; Stoica et al., 2000); some evidence suggests that changes in cell number elicited through ERα does not require the natural ligand, E2, and may be mediated by alterations in cell cycle control (Davey et al., 2007; Chow et al., 2004; Stoica et al., 2000). In addition to changes in cell number, inorganic arsenic mediated changes in endocrine signaling may lead to alterations in intracellular hormone

distribution (i.e., shift from cytosol to nucleus) if exposure occurs early in life (e.g., during gestation and early postnatal development) (Goggin et al., 2012).

Changes at the cellular level can ultimately lead to ***tissue or organ system responses*** that in this MOA include alterations in elements of the **hypothalamic-pituitary-adrenal (HPA) axis** (e.g., intracellular receptor distribution, protein glycosylation), the **hypothalamic-pituitary-gonadal (HPG) axis** (e.g., lower concentrations of gonadotropins and sex steroid hormones), **testicular toxicity, impaired spermatogenesis, toxicity to the female reproductive system**, and **hormone-dependent tissue remodeling** (i.e., morphogenesis) (Goggin et al., 2012; Chatterjee and Chatterji, 2010; Davey et al., 2008; Jana et al., 2006; Sarkar et al., 2003; Chattopadhyay et al., 1999) (Table in Section 10.2). Data supporting alterations in the HPA axis are available from a developing animal model, suggesting that early life exposures to inorganic arsenic may have particular effects at the individual level, as discussed below (Goggin et al., 2012). Still other studies have suggested endocrine-mediated effects of inorganic arsenic exposure on male and female reproductive systems (e.g. decreased reproductive tissue weight, sperm count, infertility, altered activity of ovarian and testicular enzymes, and prostate cancer), which follows from alterations in elements of the HPG axis noted above (Chatterjee and Chatterji, 2010; Rosenblatt and Burnstein, 2009; Prins, 2008; Jana et al., 2006; Pant et al., 2004; Sarkar et al., 2003; Chattopadhyay et al., 1999). Changes in morphogenesis were observed in an amphibian model of thyroid hormone (TH) activity that also has important implications for inorganic arsenic effects on TH during the perinatal period of human development (6 months of gestation through early postnatal development) (Goggin et al., 2012).

Little evidence was identified to link tissue or organ level responses to ***individual responses*** through this MOA; however, several studies suggest that alterations in GR transcription and subsequent changes in HPA axis activity, such as those outlined above, can lead to **developmental neurotoxicity** (e.g., impaired stress response, depressive-like behaviors) following developmental inorganic arsenic exposure in mice (Goggin et al., 2012; Martinez-Finley et al., 2011; Martinez-Finley et al., 2009; Martinez et al., 2008) (Table in Section 10.2). Efforts to carry out a comprehensive literature search are ongoing and may identify additional studies with data relevant to individual level responses resulting from inorganic arsenic effects on the endocrine system.

No data were identified indicating the types of responses that might occur in ***susceptible individuals*** through this MOA. Given the role of steroid receptors in this MOA, differences in receptor or steroid levels across lifestages or physiologic conditions may confer differences in response to inorganic arsenic exposures across individuals and

provide insight on potentially susceptible individuals (Bodwell et al., 2006). The influence of receptor levels is particularly important in considering developmental inorganic arsenic exposures due to the critical role that TH, RAR and other nuclear hormone receptors play during development coupled with evidence of developmental neurotoxicity in animal models of inorganic arsenic exposure (Goggin et al., 2012; Martinez-Finley et al., 2011; Martinez-Finley et al., 2009; Davey et al., 2008; Martinez et al., 2008). Thus, pregnant women and developing children may be particularly susceptible to adverse outcomes from inorganic arsenic exposure.

Responses in susceptible individuals clearly influence responses observed at the ***population level.*** To that end, findings in rodents suggesting that endocrine effects may result in **developmental neurotoxicity** are concordant with findings in the epidemiology literature that show a correlation between early life exposure to inorganic arsenic and cognitive function (Wasserman et al., 2007). Other literature supports higher incidences of **male infertility and prostate cancer** in populations exposed to inorganic arsenic, although the connections between these observations and effects on the endocrine system are less clear. Ongoing efforts to identify relevant literature may identify additional data to connect inorganic arsenic effects on the endocrine system to population level responses.

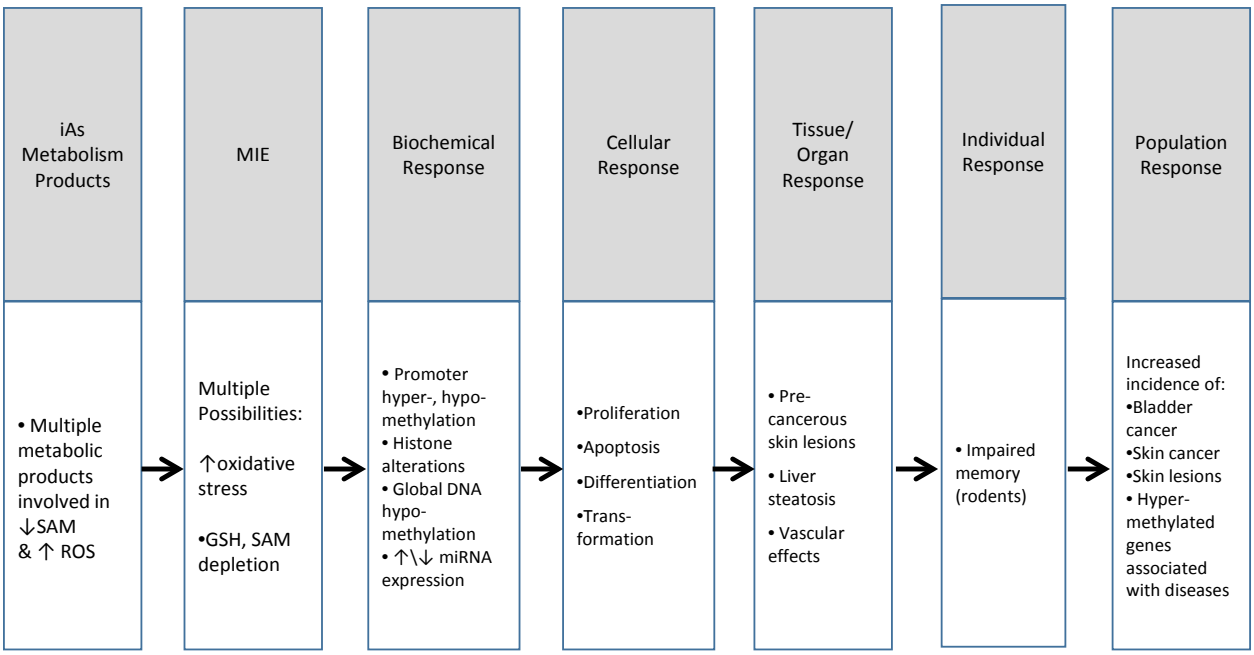
9.4 Hypothesized MOA: Effects Mediated By Epigenetic Mechanisms

Relevant Health Effects: Bladder cancer, skin cancer, skin lesions

As detailed below, several studies were identified that indicate epigenetic mechanisms may mediate some of the adverse health effects associated with exposure to inorganic arsenic (Figure 9-4). There is a broad consensus in the literature that the depletion of glutathione and S-adenosylmethionine (SAM) during cellular metabolism of inorganic arsenic species are important ***molecular initiating events (MIEs)*** of this MOA (Martínez et al., 2011; Ren et al., 2011; Reichard and Puga, 2010). In addition, inorganic arsenic can also elevate levels of reactive oxygen species (ROS), which may in turn deplete SAM, in conjunction with, or separately from SAM depletion that results from inorganic arsenic methylation. Specifically, some evidence suggests that the depletion of glutathione (GSH) due to elevated oxidative stress results in the shunting of S-adenosyl homocysteine in order to replenish GSH, through the transsulfuration pathway, and away from the synthesis of SAM, inducing a shortage of methylation cofactors (reviewed by

Reichard and Puga, 2010). Consistent with these findings and with multiple observations of GSH depletion, some investigators interpret the downstream epigenetic changes associated with inorganic arsenic exposure as mainly resulting from oxidative stress effects [(Kitchin and Conolly, 2010); see Oxidative Stress MOA Summary)].

The depletion of SAM may lead to one of the most well-studied of arsenic-associated epigenetic effects at the ***biochemical response level***, namely, changes in **DNA methylation patterns**. Like arsenic 3+ methyltransferase (As3mt), DNA methyltransferases (collectively, DNMTs) use SAM as a methyl donor. Therefore, reduced cellular SAM levels as a result of increased As3mt activity could lead to reduced DNA methylation. Several studies have found reduced levels of DNMT activity or expression in arsenic-exposed cell lines (Reichard et al., 2007; Benbrahim-Tallaa et al., 2005; Zhao et al., 1997). The observed changes in RNA expression levels suggest that factors in addition to SAM depletion may be responsible for changes in DNMT activity (Reichard and Puga, 2010).



Abbreviations: Inorganic arsenic (iAs); molecular initiating events (MIEs); glutathione (GSH); S-adenosylmethionine (SAM); microRNA (miRNA)

See Summary Text and Table for references; Figure based on Ankley et al. (2010).

Note: Figure shows a high-level summary of key events from the initial molecular interaction through a possible population level response. The arrows link each key event (e.g., individual responses lead to population responses), but do not necessarily link each specific example response (e.g., impaired memory is not linked to skin cancer). Of particular note for this MOA is that evidence at the individual level was only identified for effects related to impaired memory, even though population level responses indicate effects in other systems (e.g., bladder, skin). As the assessment development process moves forward additional evidence may provide better understanding of the key events in this MOA and the connections between them.

Figure 9-4 Hypothesized mode of action for epigenetic mechanisms underlying associated health effects of inorganic arsenic exposures.

Sufficiently reduced DNMT activity would likely inhibit cells' ability to maintain normal DNA methylation pattern and reduce the overall extent of DNA methylation. **Global DNA hypomethylation** after inorganic arsenic exposure has indeed been observed in a range of in vivo and in vitro studies (Pilsner et al., 2012; Coppin et al., 2008; Reichard et al., 2007; Benbrahim-Tallaa et al., 2005; Chen et al., 2004b; Sciandrello et al., 2004; Xie et al., 2004; Chen et al., 2001; Zhao et al., 1997) (Table in Section 10.3). Reduced DNMT activity and SAM depletion were seen in some, but not all, of these studies. A small number of studies have also reported global DNA hypermethylation in human populations and animals (Majumdar et al., 2010; Pilsner et al., 2007; Zhong and Mass, 2001), but it is not clear whether these studies had sufficient resolution to resolve truly "global" changes from promoter-specific changes, which are discussed below.

In addition to non-specific reductions in DNA methylation, numerous studies have found changes in **specific gene promoter DNA methylation** after inorganic arsenic exposure (Ren et al., 2011). DNA hypermethylation in the promoter regions of several tumor suppressor genes has been reported in human cells (Smeester et al., 2011; Chen et al., 2007a; Zhang et al., 2007; Chanda et al., 2006; Marsit et al., 2006b), and in a number of *in vivo* (Cui et al., 2006a) and *in vitro* (Jensen et al., 2008; Chai et al., 2007; Fu and Shen, 2005; Mass and Wang, 1997) studies (Table in Section 10.3). Of note, hypermethylation in the promoter regions of the tumor suppressor genes, Cdkn2a and Rassf1 were correlated with reduced mRNA expression in lung tissue of mice chronically exposed to As(V) (Cui et al., 2006a), indicating a role for epigenetic alterations in gene expression levels related to malignant transformation. In agreement with most studies analyzing global DNA methylation, hypomethylation has also been observed in Hras and ERα gene promoter regions in livers of mice exposed to As(III) (Chen et al., 2004b; Waalkes et al., 2004a; Okoji et al., 2002). After 18.5 weeks of As(III) exposure in dietary methyl deficient C57BL/6J mice, liver tissue exhibited steatosis and microgranulomas, along with Hras promoter hypomethylation, highlighting an important link between inorganic arsenic exposure and a dietary methyl deficient susceptible population (Okoji et al., 2002). Furthermore, ERα promoter hypomethylation was observed in combination with increased expression of ERα and cyclin D1 (mRNA and protein; biomarkers of hepatocellular lesions and carcinogenesis) in livers of mice chronically exposed to As(III) (Chen et al., 2004b). Taken together, the data suggest a general, but not entirely consistent, pattern of 1) promoter methylation in tumor suppressor and apoptosis-related genes, and 2) hypomethylation of proto-oncogenes and proliferation-related genes. In addition, Jensen et al. [(Jensen et al. (2009b); Jensen et al. (2008))] have observed DNA hypermethylation in promoter regions also subject to histone hypoacetylation (see below). The mechanism by which the specificity of arsenic-associated promoter methylation is established is not known (Ren et al., 2011).

A second major epigenetic response to inorganic arsenic exposure that the literature identifies is **histone protein modifications**. Histone proteins maintain the structure of chromatin and play an important role in gene transcription and repression. The most well–studied chemical modification of histones in response to inorganic arsenic exposure are changes in acetylation and methylation patterns, but evidence also shows an association between inorganic arsenic and increased histone phosphorylation (Ren et al., 2011). Changes in the acetylation pattern of H3 and H4 lysine residues after acute inorganic arsenic exposure have been reported in the following cell lines: mouse adenocarcinoma (Barr et al., 2009), human bladder (Chu et al., 2011; Jo et al., 2009; Jensen et al., 2008), human lung (Li et al., 2003), and human liver (Ramirez et al., 2008)

(Table in Section 10.3). Most *in vitro* studies report decreased lysine acetylation after inorganic arsenic exposure, which is in agreement with recent studies that described decreased H3K9 acetylation in blood cells of humans exposed to inorganic arsenic through drinking water (Arita et al., 2012; Chervona et al., 2012; Arita and Costa, 2009). However, increased H3K14 acetylation and H3S10 phosphorylation associated with c-Jun and c-Fos chromatin, along with increased expression of c-Jun and c-Fos, were observed in human fibroblasts (Li et al., 2003). c-Jun and c-Fos are important transcriptional mediators of cellular differentiation, proliferation, and apoptosis. The relevance of this finding for environmental exposures is questionable, however, because this study used high and likely non-physiologic As(III) exposures (400 µM), whereas other studies used less than 10 µM As(III). Increased histone acetylation has been shown to be associated with the inhibition of histone deacetylase activity; however the underlying mechanism of this reduced enzyme activity is not known (Ramirez et al., 2008).

Results of other histone modification experiments have been quite variable. Both increased and decreased methylation of H3 arginine and lysine residues were observed in *in vitro* and *in vivo* lung and liver models. In contrast, increased H3K9 dimethylation has been reported in human peripheral blood cells (Arita et al., 2012; Chervona et al., 2012), mouse liver (Suzuki and Nohara, 2013) and human lung adenocarcinoma cells (Zhou et al., 2008) after inorganic arsenic exposure. Of note, histone modifications associated with inorganic arsenic exposure have been reported in connection with downstream effects, including decreased p16 expression in the absence of altered mRNA expression levels (Suzuki and Nohara, 2013) and increased HMT G9a protein and mRNA levels (Zhou et al., 2008). Increased phosphorylation of H3S10 was linked with increased expression of c-Jun and c-Fos and upregulation of caspase 10 (Li et al., 2003). Taken together, studies examining histone modifications indicate that inorganic arsenic exposure mediates epigenetic alteration of DNA and histones, followed downstream alterations in gene expressions and, as discussed below, some phenotypic changes in exposed cells.

An increasing body of evidence suggests that microRNA expression is altered in response to inorganic arsenic exposure (Kaul et al., 2014; Li et al., 2012; Cao et al., 2011; Marsit et al., 2006a) (Table in Section 10.3). MicroRNAs, which generally suppress the translation of mRNA into protein and enhance mRNA degradation, are both up- and downregulated (often in the same model system) after inorganic arsenic exposure. Recent evidence links altered microRNA expression to downstream effects and adverse events. For example, the downregulation of hsa-miRNA-19a has been associated with cell growth arrest and apoptosis (Cao et al., 2011). More importantly, the upregulation of hsa-

miR-21 in response to As-induced ROS has been linked to carcinogenic transformation, a likely epigenetic mediated MOA linked to changes in microRNA expression (Ling et al., 2012). As discussed above, findings in different test systems are often inconsistent, and the correlations of epigenetic changes with downstream effects of gene expression and cell phenotype are just beginning to be elucidated.

Altered ***cellular phenotypes***, including malignant transformation, have been associated with epigenetic changes following inorganic arsenic exposure in several studies (Table in Section 10.3). In addition to the transformation of embryonic lung fibroblasts noted above (Ling et al., 2012), the malignant transformation of p53 knocked down human bronchial epithelial cells has been associated with downregulated hsa-miR-200b via increased DNA promoter methylation (Wang et al., 2011b). Jensen et al. (2009a; 2009b; 2008) also report epigenetic changes (parallel changes in DNA promoter methylation and histone acetylation) in selected genes in parallel with the development of malignant phenotype in human urothelial cells. Moreover, epigenetic alternations after inorganic arsenic exposure have been reported in connection with ***tissue or organ system responses***, including skin lesions in humans (Banerjee et al., 2013; Pilsner et al., 2009) and liver effects in mice, such as steatosis, microgranulomas, and hepatocellular carcinoma (Chen et al., 2004b; Waalkes et al., 2004a; Okoji et al., 2002). Organ system responses have been associated with both DNA hyper- (Banerjee et al., 2013) and hypomethylation (Pilsner et al., 2009; Chen et al., 2004b; Waalkes et al., 2004a; Okoji et al., 2002).

While ***individual responses*** have been widely reported after inorganic arsenic exposure, there are relatively few studies linking responses at the individual level to epigenetic changes. As discussed below, there are some data connecting health effects associated with inorganic arsenic exposures and epigenetic changes in population-based studies. One study on response at the individual level in animals did evaluate inorganic arsenic induced epigenetic changes in relation to cognitive function and found contextual memory deficits in rats exposed during gestation and early postnatal development (Martínez et al., 2011). Ongoing efforts to complete a comprehensive literature search may identify additional studies that link inorganic arsenic exposure to epigenetic changes and subsequent health effects.

Based on available mechanistic and in vivo studies, a range of factors affecting ***individual variations in susceptibility*** may relate to epigenetic mechanisms underlying adverse health effects of inorganic arsenic exposures (Table in Section 10.3). These include dietary deficiencies, life stage susceptibility, gender, genetics, and smoking. Several studies have investigated the relationships between **dietary sufficiency** and

epigenetic changes associated with inorganic arsenic exposure. Low folate status has been associated with the development of skin lesions in Bangladeshi adults (Pilsner et al., 2007), as well as Hras promoter DNA hypomethylation, steatosis and microgranulomas in livers of mice exposed to inorganic arsenic (Okoji et al., 2002). While the proposed epigenetic MOAs suggest that dietary intake of methionine and folate intake would positively correlate with DNA methylation, conflicting evidence has been reported. Associations between increases in DNA methylation and inorganic arsenic exposure were only observed in individuals with adequate folate status (Pilsner et al., 2007). Moreover, Lambrou et al. found that the exposure-response relationship between inorganic arsenic exposure and changes in DNA methylation in ALU retrotranspon elements (thought to be involved in cancer and other diseases) varied depending on folate intake (Lambrou et al., 2012). Study subjects were elderly males from the Normative Aging Study whose arsenic exposures had been relatively low. Evidence also suggests adverse effects related to folate supplementation and subsequent high fetal exposure to reactive As metabolites, where reduced fetal weights and altered fetal liver DNA methylation was observed after *in utero* exposure from mouse dams fed a high folate diet (Tsang et al., 2012).

***In utero* exposures** to inorganic arsenic have been a major focus of efforts to identify susceptible life stages for epigenetic effects of As exposure. Studies in rodents have detected DNA hypomethylation (Martínez et al., 2011; Waalkes et al., 2004a) and numerous DNA methylation changes at specific loci (Tsang et al., 2012). Interestingly, the analysis of cord blood of inorganic arsenic exposed mothers revealed the upregulation of 12 miRNAs linked to cancer, diabetes, and immune response signaling pathways (Rager et al., 2014). Limited studies have attempted to evaluate the effect of gender on epigenetic changes associated with inorganic arsenic exposure. In one study, DNA methylation status differed between genders in mice exposed to As(III) independent of cellular SAM levels (Nohara et al., 2011). Another study reported a potential **genetic susceptibility** related to epigenetic changes after inorganic arsenic exposure. In peripheral blood samples of Argentinian women, an AS3MT haplotype associated with efficient inorganic arsenic metabolism revealed increased methylation of the AS3MT gene region and reduced AS3MT mRNA expression (Engström et al., 2013). The methylation status and expression of other genes on the same haplotype block as AS3MT were also altered, being either upregulated or downregulated, and the authors suggested that these genes may also be involved in inorganic arsenic metabolism or responses to inorganic arsenic exposure.

The susceptible individual responses linked to genetic factors in different populations may shed light on ***population responses*** associated with the epigenetic mechanisms of

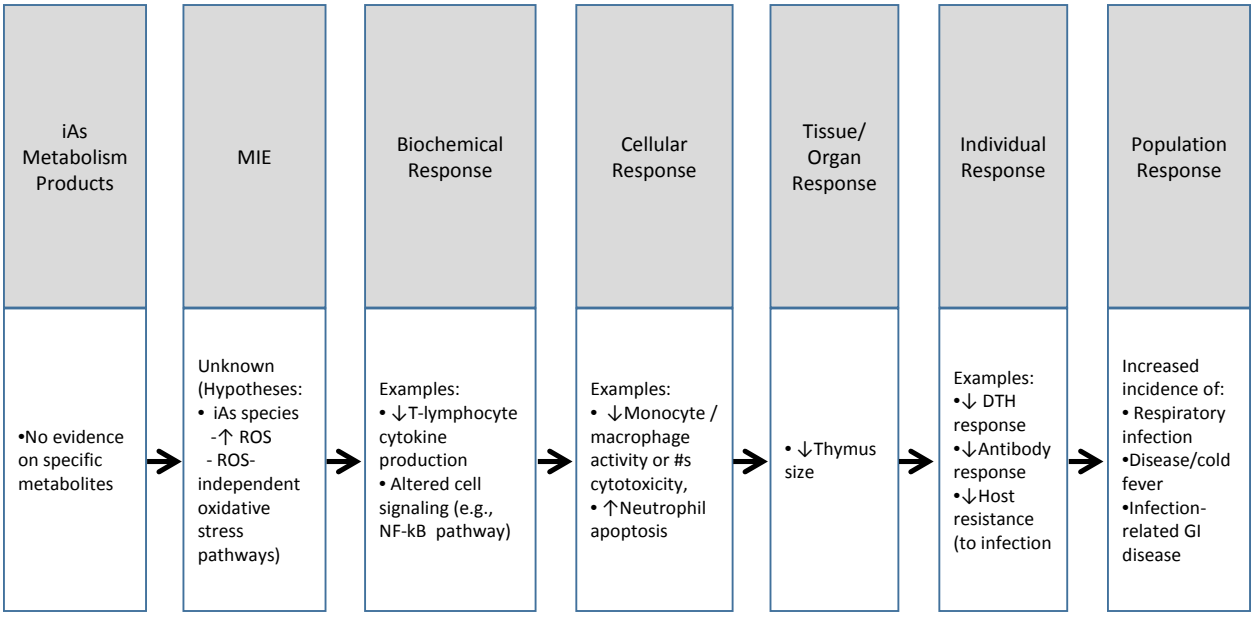
inorganic arsenic-induced adverse health outcomes. In addition, changes in DNA methylation patterns (hyper- or hypomethylation) have be identified in humans with skin and bladder cancers (Chanda et al., 2006; Marsit et al., 2006b). Pilsner et al. (2009) found a relationship between global DNA hypomethylation and the risk of inorganic arsenic-induced skin lesions. Smeester et al. (2011) identified 182 genes whose promoter regions were consistently hypermethylated in a Mexican population with arsenicosis symptoms (skin lesions). Notably, they identified a network of 17 highly-methylated tumor suppressor and related genes (the "suppressome"), and suggested that downregulation of these genes increased the risk of inorganic arsenic-associated adverse effects. Future research may strengthen existing evidence related to susceptible individuals, including those with dietary methyl deficiencies or genetic polymorphisms, and reveal additional factors that influence subsequent population level responses.

9.5 Hypothesized MOA: Immune Mediated Effects

Relevant Health Effects: Suppression of humoral immunity (i.e., decreased antibody response), Suppression of innate immunity (decreased macrophage function), Respiratory infection, Gastrointestinal infection, Contact hypersensitivity response

Several adverse health effects following exposure to inorganic arsenic may result from events mediated by the immune system, including: suppression of humoral immunity (decreased antibody response), suppression of macrophage function, and other aspects of innate immunity (Figure 9-5). The ***molecular initiating event*** (MIE) for arsenic immune-mediated effects is unknown, although available literature indicates that it likely includes a pathway that leads to reactive oxygen species (ROS) generation and a pathway that is unrelated to ROS. Because oxidative stress (and the generation of ROS) is covered in a separate MOA, it will only be discussed briefly here with an indication as to where it may play a role in immune-mediated effects. Specifically, there is evidence that apoptosis of T-cells [e.g., (Gupta et al., 2003)] as well as monocytes/macrophages [e.g., (Park et al., 2003)] is ROS dependent indicating that oxidative stress may contribute to effects on both humoral and innate immunity. However, the molecular initiating events for most immune and immune-mediated effects are unknown with evidence that some do not rely on ROS production. For example recent studies by Bourdonnay et al. (2009) have demonstrated that arsenic trioxide alters macrophage gene expression in human macrophages (prepared from peripheral blood mononuclear cells (PBMC) from healthy donors) through redox-sensitive signaling pathways that are independent of ROS production.

There are a number of ***biochemical responses*** within immune cells that are likely to contribute to immune-mediated inorganic arsenic effects (Table in Section 10.4). First, there is considerable evidence that inorganic arsenic exposure decreases the production of cytokines by stimulated T-lymphocytes, particularly secretion of interleukin-2 (IL-2) demonstrated at the protein and mRNA level. Inorganic arsenic not only decreased IL-2 secretion in culture conditions with T-cell superantigens (e.g., PHA or ConA), but more importantly in studies where T-cells were stimulated with antibodies to CD3/CD28, which mimic the biological function of natural antigens activating T-cells through T-cell receptor engagement. Following activation, IL-2 stimulates survival of antigen-specific T-cells, expansion of antigen-selected T-cells, differentiation, and development of immunologic memory. Therefore, arsenic-induced inhibition of IL-2 as well as decreased T-cell proliferation [e.g., (Vega et al., 1999; Gonsebatt et al., 1994)] suggests altered biochemical responses that would contribute to reduced antibody responses. Evidence for reduced IL-2 secretion includes populations with chronic inorganic arsenic exposure (Biswas et al., 2008; Soto-Peña et al., 2006) as well as in vitro arsenic exposure of cells from healthy individuals (Morzadec et al., 2012; Galicia et al., 2003; Vega et al., 1999) mouse in vivo and in vitro studies (Cho et al., 2012; Soto-Peña and Vega, 2008; Conde et al., 2007), and from non-mammalian models including chickens (Das et al., 2011).



Abbreviations: Inorganic arsenic (iAs); molecular initiating event (MIE); reactive oxygen species (ROS); delayed-type hypersensitivity (DTH)

See Summary Text and Table for references; figure based on Ankley et al. (2010).

Note: Figure shows a high-level summary of key events from the initial molecular interaction through a possible population level response. As the assessment development process moves forward additional evidence may provide better understanding of the key events in the MOA and the connections between them.

Figure 9-5 Hypothesized mode of action for effects mediated by the immune system.

There is also consistent evidence that inorganic arsenic reduces T-cell secretion of other cytokines including interferon-gamma (IFN-γ) and less consistent evidence for reduced IL-4, IL-5, IL-10, and IL-12. Together, evidence suggests that inorganic arsenic alters a wide variety of immune cellular signals and pathways that relate to both innate and humoral immunity. In general these cytokines have multiple roles that impact both innate and humoral immune responses. For example, IFN-γ is important for antigen presentation by macrophages and reductions in IFN-γ may therefore contribute to reduced antibody response. IFN-γ also directly inhibits viral replication and contributes to multiple aspects of the innate immune system including natural killer (NK) cell activity and lysosome activity of macrophages.

Other biochemical responses include altered cell signaling in NF-κB (Zheng et al., 2012; Lemarie et al., 2006) and decreased transcription factor ERG2 (Bourdonnay et al., 2009). Lemarie et al. (2006) reported that arsenic trioxide induced apoptosis of human peripheral blood derived monocytes during macrophage differentiation via a NF-κB-

dependent pathway. Bourdonnay et al. (2009) also reported arsenic trioxide-associated inhibition of human macrophage differentiation. The authors suggest that the observed effects on macrophages are likely to be mediated by reduced expression of EGR2, which was independent of ROS production.

There are a number of studies reporting ***cellular phenotypic changes*** associated with inorganic arsenic exposure that support a link between biochemical responses and tissue or individual responses for immune-mediated arsenic effects. Many of the studies outline effects on monocytes or macrophages including decreased recruitment in mice [e.g., (Patterson et al., 2004)], reduced differentiation in humans (Lemarie et al., 2006), altered morphology in mice and humans (Banerjee et al., 2009; Bishayi and Sengupta, 2003), and increased apoptosis in mice and humans (Lemarie et al., 2006; Park et al., 2003; de la Fuente et al., 2002). Phenotypic changes also included adverse changes in measures of macrophage functional responses including decreased adhesion, reduced chemotaxis, decreased phagocytosis of bacterial challenge, and reduced generation of ROS (Banerjee et al., 2009; Aggarwal et al., 2008; Ghosh et al., 2006; Arkusz et al., 2005; Bishayi and Sengupta, 2003; Sengupta and Bishayi, 2002). These cellular phenotypic changes were associated with inorganic arsenic exposure in vitro to cells from healthy individuals [e.g., (de la Fuente et al., 2002)], experimental animals exposed to inorganic arsenic in drinking water [e.g., catfish (Ghosh et al., 2006); chickens (Aggarwal et al., 2008) and mice (Sengupta and Bishayi, 2002)], and humans from inorganic arsenic-exposed populations [e.g., (Banerjee et al., 2009)]. There are several studies that also reported increased apoptosis of human neutrophils (Binet and Girard, 2008), human T-cells (Gupta et al., 2003), and mouse B-cells (Harrison and McCoy, 2001) following in vitro arsenic exposure.

There are primary (i.e., bone and thymus) and secondary (spleen, lymph nodes, and mucosal associated tissue) immune organs; however, immune cells are distributed throughout the body and travel extensively through blood and lymph. Therefore there may be important system-wide changes in local cell populations or function that are not readily apparent when categorized at a ***tissue or organ response*** level. The one organ-level arsenic-related response observed that is likely to contribute to immune-mediated arsenic effects is decreased size of the thymus, which as the site of T-cell maturation is an important part of humoral immunity. As a single parameter, thymus size is an immune cell measure with low predictive value for immunotoxicity; however it may lend support to altered immune function indicated by other assays (Luster et al., 1992), particularly immune functional measures such as T-cell mediated antibody response. Thymus size in children from the Metlab region of Bangladesh was negatively associated with maternal

arsenic exposure determined at 8 and 30 weeks of gestation (Moore et al., 2009; Raqib et al., 2009). Decreased absolute, but not relative, thymus size was also reported in chickens exposed to 3.7 ppm sodium arsenite in drinking water (Aggarwal et al., 2008).

There are multiple inorganic arsenic-associated ***individual responses*** that represent adverse functional immune changes as part of the immune-mediated arsenic effects. Multiple studies report arsenic-associated suppression of the T-cell dependent antibody response or response to a T-cell antigen such as sheep red blood cells (SRBCs) or keyhole limpet hemocyanin (KLH). Male mice exposed to 1 or 50 μg/m^3 arsenic trioxide for 14 days, or 0.5-10 ppm sodium arsenite in drinking water had reduced T-cell dependent antibody response to SRBC (Nain and Smits, 2012; Blakley et al., 1980). Male Wistar rats exposed to sodium 0.4-40 ppm arsenite in drinking water had reduced IgG antibody response to KLH, but no change in IgM response (Burchiel et al., 2009). Arsenic-associated reductions in antibody response to SRBCs were also observed in catfish as was decreased antibody response to antigen challenge with virus (F-strain RD-F) in chickens (Aggarwal et al., 2008; Ghosh et al., 2007a).

Several studies report that inorganic arsenic exposure suppresses the delayed type hypersensitivity (DTH) response. These hypersensitivity assays all require coordination between multiple cytokine signals and two principal cell types: antigen presenting cells (e.g., macrophages or Langerhans cell) and T-cells. Sankar et al. (2013) reported that exposure to 25 ppm sodium arsenite in drinking water for 42 days resulted in decreased DTH to KLH measured by changes in footpad thickness in male Wistar rats. Savabiesfahani et al. (1998) reported suppression of the related endpoint of decreased phytohemagglutinin hypersensitivity response by rump skin fold thickness after exposure of cotton rats to 5 or 10 ppm sodium arsenite. A decreased DTH response to DNCB or PHA-P was also observed in chickens exposed to 3.7 ppm sodium arsenite for 60 days (Aggarwal et al., 2008). Inorganic arsenic exposure of mice at 50 mg/l for 4 weeks was associated with reduced contact hypersensitivity response following sensitization with 2, 4-dinitroflurobenzene (DNFB) (Patterson et al., 2004).

Host resistance assays such as the response to viral challenge requires integration of innate and adaptive immune response. For example, early reactions to viral challenge include aspects of innate immunity such as recruitment of macrophages and neutrophils to the lung to initiate phagocytosis, secrete cytokines and begin the process of antigen processing and presentation for a strong humoral immune response. Mice exposed to 100 ppb sodium arsenite in drinking water displayed a significantly altered pattern of neutrophil and macrophage recruitment into the lung as determined by bronchoalveolar lavage fluid (BALF) with decreased neutrophils and macrophages through 3 days post

infection and increased numbers of macrophages and neutrophils 7 days post infection (Kozul et al., 2009). The resulting virus titers in inorganic arsenic exposed mice were higher as were other signs of morbidity to respiratory influenza A (H1N1) virus. Inorganic arsenic exposure is also associated with decreased bacterial clearance in multiple animal models including mice (Bishayi and Sengupta, 2003), catfish (Ghosh et al., 2007a), and zebrafish (Nayak et al., 2007).

Suppression of host resistance assays, delayed-type hypersensitivity, and T-cell dependent antibody response are considered among the best assays for determining chemical immunotoxicity, particularly when there are indications that multiple functional parameters are effected (WHO, 2012; U.S. EPA, 1998), and there is evidence that inorganic arsenic exposure is associated with immune suppression by all three measures.

Few **susceptible individual response** factors have been identified that are likely to contribute to immune-mediated inorganic arsenic effects. However, given the importance for cytokine communication and coordination of immune function, gene polymorphisms relating to cytokine function are logical candidates. Banerjee et al. (2011) reported an association between polymorphisms in TNF-α (-308G/A) and IL-10 (-3575T/A) promoters and inorganic arsenic-associated respiratory effects and conjunctivitis. Individuals with GA/AA (-308 TNF-α) and TA/AA (-3575 IL10) genotypes were at higher risk of developing inorganic arsenic-associated conjunctivitis and respiratory effects, as well as inorganic arsenic-induced skin lesions. In a related study by the same research group, Bhattacharjee et al. (2013) reported that polymorphisms in the NALP2 gene also modify risk of inorganic arsenic-associated respiratory disease.

Inorganic arsenic-associated increases in respiratory disease, incidence of colds or fever, and diarrhea represent **population level responses** with a strong link to immune-mediated inorganic arsenic effects. Increased relative risk of lower respiratory tract infection for children of mothers with higher urinary arsenic levels was reported in several studies of the Matlab region of Bangladesh (Rahman et al., 2011; Raqib et al., 2009). A similar increase in relative risk of both upper and lower respiratory tract infection and number of colds treated with prescription medications was reported in children from a New Hampshire Birth Cohort correlated with maternal urinary arsenic levels at 24-28 weeks of gestation (Farzan et al., 2013). The Rahman et al. (2011) study reported an increased relative risk of diarrhea in the children of arsenic-exposed mothers in Bangladesh and the Farzan et al. (2013) study reported a non-significant arsenic-associated increase in diarrhea symptoms lasting two or more days or requiring doctor visit [RR=1.9 (95% CI: 0.9, 3.9) and RR=3.5 (95% CI: 0.8, 15.4)]. Although most of these disease-related endpoints were in children, one of the Bangladesh cohorts reported

increased number of days with fever and increased number of days of diarrhea in the pregnant mothers (Raqib et al., 2009).

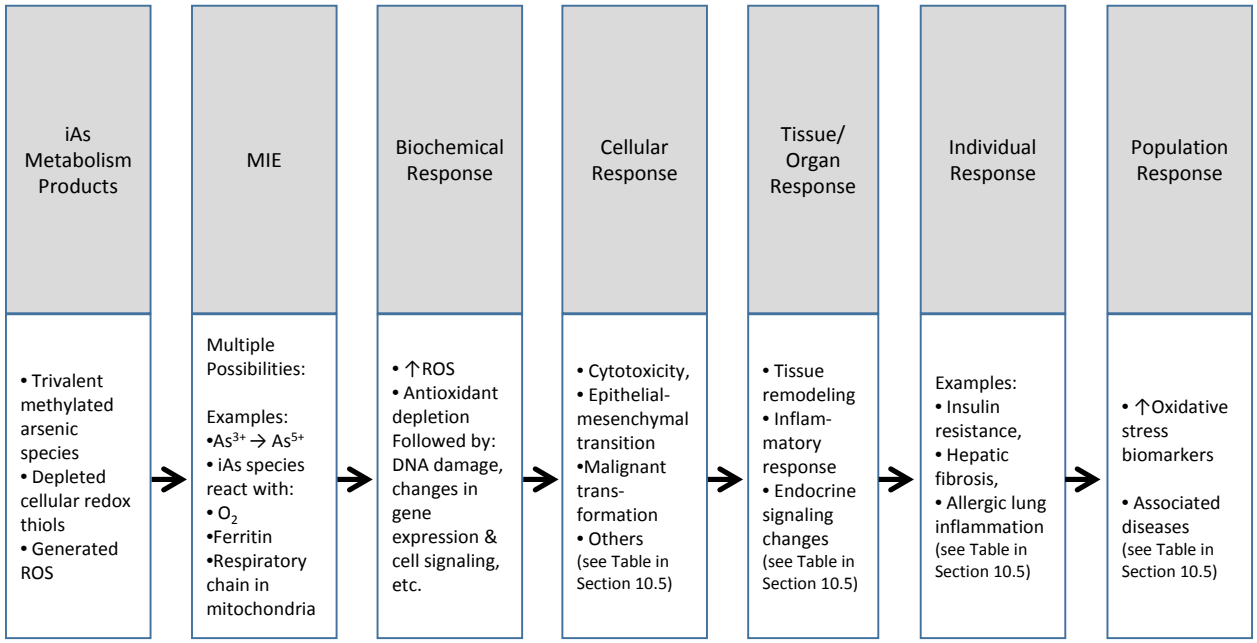
9.6 Hypothesized MOA: Oxidative Stress

Relevant Health Effects: Cardiovascular Disease, Diabetes, Liver Disease, Lung Cancer, Bladder Cancer, Neurotoxicity, Non-Malignant Respiratory Disease, Pregnancy Outcomes, Renal Disease, Skin Cancer, and Skin Lesions

As discussed in the Preamble, mammalian metabolism of inorganic arsenic involves a cascade of oxidation-reduction reactions whose net results are (1) generation of trivalent methylated species, (2) depletion of cellular thiols that are involved in maintaining cellular redox balance, and (3) the generation of reactive oxygen species (ROS). Several adverse health effects following exposure to inorganic arsenic may thus result from events mediated by oxidative stress (Flora, 2011; Jomova et al., 2011; Kitchin and Conolly, 2010) (Figure 9-6). The ***molecular initiating event (MIE)*** in this MOA is a topic of ongoing research but likely includes one of the following: 1) intermediate arsine species (e.g., dimethylarsine) react with molecular oxygen, 2) methylated arsenic species react with ferritin, 3) arsenite oxidizes to arsenate, and 4) inorganic arsenic interacts with complexes in the mitochondrial electron transport chain and/ or antioxidant enzymes (e.g., nicotinamide adenine dinucleotide phosphate-oxidase [NADPH oxidase]) (Li et al., 2014; Flora, 2011).

While multiple MIEs are possible for this MOA, each one will result in a biochemical response that consists of perturbing the redox balance in the cell through: 1) generation of ROS (e.g., superoxide, H2O2, hydroxyl radical), and 2) depletion of antioxidant defenses (e.g., glutathione [GSH], ascorbate, superoxide dismutase) (Flora, 2011; Jomova et al., 2011; Kitchin and Conolly, 2010; De Vizcaya-Ruiz et al., 2009). Each set of responses, ROS generation and redox depletion, can initially involve a separate set of reactions, but both are intricately linked such that elevated ROS levels can deplete redox enzymes and vice versa (Flora, 2011; Jomova et al., 2011; Kitchin and Conolly, 2010). Moreover, although the generation of ROS or depletion of antioxidant defenses may occur in multiple tissue types, the subsequent redox response is likely tissue dependent due to differences in constitutive levels of redox enzymes and peptides across cell types (e.g., higher constitutive glutathione levels in lung fibroblasts compared to keratinocytes) (Snow et al., 2005). In turn, while oxidative stress may be a MOA common to several

adverse health effects, the context (i.e., cell type) in which oxidative stress occurs will influence the health effect(s) that are ultimately observed.



Abbreviations: Inorganic arsenic (iAs); molecular initiating event (MIE); reactive oxygen species (ROS)

See Summary Text and Table for references; Figure based on Ankley et al. (2010).

Note: Figure shows key events from the initial molecular interaction through a possible population level response. Note that arrows link each key event (e.g., individual responses lead to population responses), but do not necessarily link each specific example response (e.g., insulin resistance is not linked to all of the diseases included in the Table in Section 10.5). As the assessment development process moves forward additional evidence may provide a better understanding of the key events in this MOA and the connections between them.

Figure 9-6 Hypothesized mode of action for effects mediated by oxidative stress.

To that end, numerous ***biochemical*** responses can occur within cells following the generation of ROS and depletion of antioxidant defenses, including changes in: protein expression, enzyme activity, lipid oxidation, DNA damage, gene expression and cell signaling (Table in Section 10.5). For instance, alterations in protein expression levels have been observed in multiple tissue types. While observations of increased protein expression levels related to antioxidant defense (e.g., Cu/Zn Superoxide dismutase [SOD], nuclear factor [erythroid-derived 2]-like 2 [Nrf2]) (Zhao et al., 2012; Zheng et al., 2012; Li et al., 2011) and DNA repair (e.g., DNA polymerase β) (reviewed in Snow et al., 2005) may occur across multiple cell types, other observations of elevated protein levels may be specific to specific cells (e.g., Platelet endothelial cell adhesion molecule

[PCAM-1]) (Straub et al., 2008). Cell-type specific changes in protein expression or other biochemical responses once again highlight how one MOA may play a role in multiple adverse health outcomes and provide insight in subsequent steps of the assessment development process (see the Inorganic arsenic ADP for more information).

For many of the biochemical responses noted above, the concentration and duration of inorganic arsenic exposure, and subsequent redox imbalance, may influence the ultimate cellular response. Based on the literature reviewed, there appears to be a possible pattern of generally adaptive cellular responses (e.g., increases in DNA base excision repair genes and antioxidant enzymes) at relatively low exposures, whereas higher concentrations may result in adverse cellular responses (e.g., decreases in DNA excision repair proteins) (Snow et al., 2005). The exposure at which disruption of cellular homeostasis occurs varies greatly across cell lines, and thus the specific concentration range that confers adaptive versus adverse cellular responses is a topic of ongoing research (Clewell et al., 2011; Flora, 2011; Gentry et al., 2010). Similarly, the changes in protein expression, enzyme activity, or DNA damage can be very time-dependent [e.g., elevated DNA repair enzyme activity at ≤ 48 hrs of inorganic arsenic exposure, compared to basal activity levels after72-120 hrs exposure (Snow et al., 2005)] (Medeiros et al., 2012; Clewell et al., 2011; Eblin et al., 2008; Eblin et al., 2006).

Separate from the consideration of exposure duration is the duration of a biochemical response that inorganic arsenic may elicit in a cell. Two aspects of response duration are important to examine. First, short-lived, reversible responses such as elevated ROS levels likely lead to distinct outcomes from prolonged, irreversible responses such as DNA damage or epigenetic alterations that persist after inorganic arsenic exposure is stopped (Flora, 2011; Wnek et al., 2009). Second, inorganic arsenic exposure may modulate the natural duration of a response, thus turning an adaptive response to an adverse response. For instance, evidence suggests that inorganic arsenic exposure may result in prolonged activation of the Nrf2 transcription factor pathway compared to when the pathway is activated by natural compounds (e.g., sulforaphane, tert-butylhyrdoquinone) (reviewed in Lau et al., 2013). The Nrf2 pathway is activated by oxidative stress and plays a key role in antioxidant defense; however, prolonged activation of the Nrf2 pathway can lead to sustained cell growth and is associated with cancer in several tissues (e.g., breast, bladder, skin) (reviewed in Lau et al., 2013). Recent data indicate that inorganic arsenic exposure may mimic constitutive Nrf2 activation found in several tumor types (reviewed in Lau et al., 2013). The mechanism through which inorganic arsenic exposure leads to subsequent activation of Nrf2 is an area of ongoing research; yet, evidence suggests that unlike natural compounds, which activate Nrf2 by inhibiting its ubiquitination through

direct interaction with Keap1 (Kelch-like ECH associated protein 1), inorganic arsenic may activate Nrf2 through a Keap1-independent mechanism (reviewed in Lau et al., 2013). Further, data indicate that Nrf2 activators which act through interaction with KEAP1 can mitigate toxic effects of inorganic arsenic exposure both in vitro and in vivo (Tao et al., 2013; Zhao et al., 2012; Wang et al., 2007b). Data from multiple cell types suggest that the Nrf2 pathway plays a critical role in antioxidant response to inorganic arsenic exposure (see examples in the Table in Section 10.5) (reviewed in Lau et al., 2013). As discussed further below, data also suggest that individuals with genetic or epigenetic alternations in the Nrf2 pathway may be more susceptible to inorganic arsenic exposure. Together, data suggest that Nrf2 plays a critical, though complex, role in inorganic arsenic mediated oxidative stress response and subsequent health effects.

Similar to observations of prolonged Nrf2 activation, data also suggest that inorganic arsenic promotes stabilization of the transcription factor HIF-1α; thus leading to prolonged transcriptional activation of downstream targets (e.g., vascular endothelial growth factor [VEGF]) (Li et al., 2014). Downstream targets of HIF-1 α can play a key role in malignant transformation and carcinogenesis by promoting angiogenesis, dedifferentiation, and glycolysis (Li et al., 2014). Prolonged HIF-1α activation following inorganic arsenic exposure is dependent on increases in ROS produced primarily by the mitochondrial electron transport chain, possibly through inorganic arsenic activation of NADPH oxidase at the cell surface (Li et al., 2014). Together with data on Nrf2 activation, evidence that inorganic arsenic perturbs HIF-1α transcriptional activity via ROS production provides insight on how subsequent changes at the cellular or tissue/ organ levels may be quite distinct despite being initiated through a common MOA.

Biological responses such as those discussed above can lead to a several ***cellular responses***, such as **cell death, malignant transformation, or epithelial-mesenchymal transition (EMT)** (Table in Section 10.5). For example, elevated levels of apoptosis have been observed in multiple cell types across in vitro and in vivo models (e.g., Zhao et al., 2012; Zheng et al., 2012). In contrast, EMT or other changes in cell membrane structures represent phenotypic changes that are likely more unique to particular cell types (i.e., epithelial cells). Importantly, manifestation of phenotypic changes in one cell type (i.e., epithelial cells) may be informative for understanding adverse effects in ***multiple tissue or organ systems***. For instance, data from Straub et al. (2008) show lower levels of membrane porosity due to elevated cell-junction protein expression (PECAM-1) in liver sinusoidal epithelial cells, which may also have relevance for understanding vascular remodeling in the cardiovascular system following inorganic arsenic exposures. Other tissue or organ level responses associated with oxidative stress following inorganic

arsenic exposures include **inflammatory response, endocrine signaling, and vascular remodeling** (Table in Section 10.5).

The types of organ or tissue level responses noted above are associated with adverse health outcomes at the level of the ***individual response***. Adverse health effects for which there is evidence of association with oxidative stress response following inorganic arsenic exposures include: **bladder cancer, cardiovascular disease, diabetes, liver disease, lung cancer, neurotoxicity, non-malignant respiratory disease, pregnancy outcomes, renal disease, skin cancer, and skin lesions**. The level of evidence supporting the various steps of the oxidative stress MOA (i.e., from molecular initiating event to adverse outcome) is variable. Based on an initial literature review, health outcomes with data available across multiple points in the oxidative stress MOA include: cardiovascular disease, lung inflammation, and skin disease (cancer or lesions). The identification of additional literature in an ongoing literature search may provide more support across the MOA for other health outcomes, or these may represent areas for future research. Importantly, information on an oxidative stress MOA for one health effect may provide insight on how this MOA could apply to other health effects. For instance, data suggest that inorganic arsenic can activate the epidermal growth factor receptor (EGFR) through the generation of ROS, and thus data showing EGFR activation in both an in vitro model of human lung cells and serum samples from liver cancer patients may provide insight on the role of this MOA in both lung and liver cancers [(Sung et al., 2012; Wu et al., 1999), reviewed in (Flora, 2011)]. In addition, multiple MOAs may be relevant for some health outcomes such as hepatotoxicity, which is associated with inflammatory response and metabolic changes as well as oxidative stress (reviewed in Flora, 2011); data also suggest that the oxidative stress may act interdependently with a MOA involving sulfhydryl protein binding in the development of bladder cancer following inorganic arsenic exposures (Wnek et al., 2011). Finally, mechanisms involved in the oxidative stress MOA [e.g., activation of mitogen activated protein kinase [MAPK] signaling pathway (Ling et al., 2012)] may subsequently influence epigenetic mechanisms, and thus interact with the epigenetic MOA (see Epigenetic Summary for details). Further research may provide greater understanding of how the oxidative stress MOA interacts with other MOAs in health outcomes associated with inorganic arsenic exposures.

Additional information on interactions between the oxidative stress MOA and other factors may be particularly useful in identifying ***susceptible individual responses***. Current data support a key role for Nrf2 pathway activation (examples in the Table in Section 10.5) (reviewed in Lau et al., 2013); where data suggest inorganic arsenic exposure may lead to prolonged pathway activation that is similar to constitutive

activation of the pathway associated with skin squamous cell carcinoma in humans (Kim et al., 2010 cited in, Zhao et al., 2012). In turn, individuals with mutations in the Nrf2 pathway (particularly Nrf2 or KEAP1) that confer constitutive activation of the pathway may have higher levels of susceptibility following inorganic arsenic activation of the pathway (Zhao et al., 2012). In addition, elevated levels of NADPH oxidase activity in in vitro and in vivo liver models suggests that genetic or epigenetic alterations of this enzyme could influence individual response to inorganic arsenic exposure (Straub et al., 2008). Indeed, polymorphisms in the NADPH oxidase p22 subunit are hypothesized to contribute to inorganic arsenic-related hypertension in Taiwan [(Hsueh et al., 2005) as cited in (Straub et al., 2008)]. Additional factors that may interact with this MOA include diabetes, smoking, alcohol and co-exposures to cadmium (Table in Section 10.5). Future research may identify other factors that influence individual susceptibility and subsequent population level responses.

The prevalence of the genetic factors noted above in different populations may provide insight on differences in ***population responses*** to inorganic arsenic exposure for health outcomes like skin cancer or cardiovascular disease. Recent work demonstrates that biomarkers of oxidative stress (e.g., malondialdehyde or other lipid peroxidation products, 8-oxo-G, 8-Hydroxy-guanine or other oxidative DNA damage products) can help connect population level responses to the occurrence of adverse health effects mediated through this MOA (reviewed in Flora, 2011; De Vizcaya-Ruiz et al., 2009). Several studies have thus used biomarkers to confirm an association between inorganic arsenic exposure and elevated oxidative stress [e.g., (Pi et al., 2002; Wu et al., 2001)]. However, associations between disease in populations exposed to inorganic arsenic and oxidative stress still primarily rely on observational population studies combined with indicators of oxidative stress in in vitro and/or in vivo studies in cell or tissue types relevant to the disease (e.g., cardiomyocytes for cardiovascular disease). Despite the observed associations between oxidative stress biomarkers and population health outcomes, a clear connection between inorganic arsenic-induced elevations in oxidative stress and subsequent disease is still lacking and contributions from other MOAs cannot be ruled out.

10 PRELIMINARY MECHANISTIC AND SUSCEPTIBILITY DATA TABLES

10.1 Preliminary Data on Effects Mediated By Cytotoxicity and Regenerative Proliferation

Relevant Health Effects: Bladder, lung, and skin cancer

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Molecular Initiating events					
Reactions with GSH and other non-protein thiols	Glutathione, cysteine, lipoic acid conjugates	Many	Humans, rodents, in vitro	Environmentally relevant and higher exposures	(Cohen et al., 2013)
Reaction with thiols/ dithiols in specific proteins	Inorganic arsenic binding with tubulin, keratin, ER-α and related receptors, PARP-1, thio-redoxin reductase, As3mt, KEAP-1, many studies of zinc finger proteins, peptides; IκB kinase; EGFR, Shc; tyrosine phosphatases, ubiquitination enzymes; XPA, XPD (NER enzymes)	Not applicable	In vitro binding of As(III) to synthetic peptides	Kds =~1-30 µg/L (↓Kd with ↑cysteine residues)	(Kitchin and Wallace, 2008, 2005), (Qin et al., 2008)
	Reduced PARP activity, restored by co-incubation with Zn	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (12 -52 wks)	(Wnek et al., 2011; Wnek et al., 2009)
Biochemical Responses					
See summary text					(Cohen et al., 2013)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Cellular Responses					
Cytotoxicity/ viability	24-hour viability (mitochondrial dehydrogenase assay)	Urothelium (Human)	UROTSA, other cell lines	Arsenite IC_{50} for UROTSA = 17.8 µM, 3.2 µM for bronchial cells, 10 µM for rat hepatocytes, >20 µM for human hepatocytes, keratinocytes (24 hr)	(Styblo et al., 2000)
Cytotoxicity/ viability (*continued)*	24-hour viability (mitochondrial dehydrogenase assay)	Multiple	Primary human, rat hepatocytes, 13 mam-malian cell lines	IC_{50}s (24 hrs): As(III) = 1-100 µM; MMA(III): 0.4 - 5.5 µM; DMA(III): 0.4 - >20 µM; most sensitive cell line: MB4 (human leukemia-derived)	(Styblo et al., 2000)
	Cell viability (light microscopy); 95% mortality at low exposure, >99% mortality at two highest exposures	Urothelium (Human)	UROtsa cells	1 µM As(III) (30 – 48 days) 4, 8 µM As(III) (30 days)	(Sens et al., 2004)
	Viability (MTT) assay	Urothelium (Human)	UROtsa cells	IC_{50} ~5 µM MMA(III) (24-72 hr) "threshold" for viability & morphology changes: ~2 µM	(Bredfeldt et al., 2006)
	Viability ↓ 42% (Trypan blue assay) *reduction, partially abolished by ROS scavengers	Urothelium (Human)	UROtsa cells	1 µM As(III) (24 hr)	(Eblin et al., 2008)
	Viability ↓ (Trypan blue assay) *reduction, partially abolished by NADPH oxidase inhibitor, but other antioxidants	Urinary bladder epithelium (Rat)	MYP3 rat cell line	1 µM As(III) (3 days)	(Suzuki et al., 2009)
	Viability ↓ (Trypan blue assay)	Urinary bladder epithelium (Rat)	MYP3 rat cell line	LC50: 0.75 µM As(III) (3 days)	(Suzuki et al., 2010)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
		Ureter epithelium (Human)	1T1 human cell line	8.3 µM As(III) (3 days)	
Proliferation	Reduced doubling time (43.1 hr to 22.1 hr)	Urothelium (Human)	UROtsa cells	1 µM As(III) (>60 days)	(Sens et al., 2004)
	Reduced doubling time (42 hr to 27 hr)	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (12weeks)	(Bredfeldt et al., 2006)
	Reduced doubling time (42 hr to 21 hr)	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (52 wks)	(Bredfeldt et al., 2006)
	↑thymidine uptake ↑S-phase cells ↓G_0/G_1 cells	Urothelium (Human)	UROtsa cells	2 or 4 µM sodium arsenite (48-72 hr) 2 or 4 µM sodium arsenite (24 hr)	(Simeonova et al., 2000)
Malignant transformation	Colony formation in soft agar, tumor formation after hetero-transplantation	Urothelium (Human)	UROtsa cells	1 µM As(III) (60 days, followed by repeated passages in As-free medium)	(Sens et al., 2004)
	Colony formation in soft agar	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (24 or 52 wks)	(Bredfeldt et al., 2006)
	Differentiation to squamous epithelium with poorly defined cell membranes, multinucleate cells; tumor formation after hetero-transplantation in SCID mice; ↑proliferative biomarker (Ki-67) in tumors	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (52 wks)	(Bredfeldt et al., 2006)
Tissue/ Organ Responses					
Tissue Cytotoxicity/ Necrosis	Mild-moderate urothelial cytotoxicity (observed by scanning electron microscopy [SEM])	Urothelium (Rat; Mouse)	F344 rats, C57BL/6 mice	100 µg/L As(III) in drinking water (2 wks) ; or 50-400 µg/g in diet (2-10 wks)	(Suzuki et al., 2008)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	Urothelial cytotoxicity, (observed by SEM) *Cytotoxicity reduced by NADPH oxidase inhibitor, apocyanin(250 mg/L)	Urothelium (Rat)	F344 rats (Female)	100 ppm As(III) in diet (20 days)	(Suzuki et al., 2009)
Tissue Cytotoxicity/ Necrosis (continued)	Urothelial cytotoxicity, necrosis (observed by SEM)	Urothelium (Rat)	F344 rats (Female)	Dose-response ~10-50 ppm As(III) in diet (5 wks) (NOEL: 1-10 ppm; significant at ≤ 50 ppm)	(Suzuki et al., 2010)
	Urothelial cytotoxicity, necrosis (observed by SEM) *cytotoxicity in KO compared to WT in same treatment groups	Urothelium (Mouse)	Wild Type (WT) and arsenic methyl-transferase (As3mt) KO mice (Female)	100 ppm As(III) in diet (6 days), followed by 50 ppm in drinking water (3 days)	(Yokohira et al., 2010)
	Urothelial cytotoxicity, necrosis (observed by SEM) *cytotoxicity in KO compared to WT in same treatment groups	Urothelium (Mouse)	WT and As3mt KO mice (Female)	10-25 ppm As(III) in drinking water (4 wks)	(Yokohira et al., 2011)
	Mild-moderate urothelial cytotoxicity (observed by SEM) *severity increased over time	Urothelium (Rat)	F344 rats (Female)	100 ppm As(III) in drinking water (6 hr-14 days)	(Arnold et al., 2013)
		Urothelium (Mouse)	C57BL/6 WT and As3mt KO mice (Female)	25 ppm As(III) in drinking water (6 hr – 14 days)	
Tissue regeneration/ Hyperplasia	Mild-moderate urothelial hyperplasia (male and female rats, male mice)	Urothelium (Rat; Mouse)	F344 rats; C57BL/6 mice	100 µg/L As(III) in water; 50-400 µg/g in diet (2-10 wks)	(Suzuki et al., 2008)
	Urothelial hyperplasia *No effect of co-exposure to NADPH oxidase inhibitor	Urothelium (Rat)	F344 rats (Female)	100 ppm As(III) in diet (20 days)	(Suzuki et al., 2009)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	Urothelial hyperplasia	Urothelium (Rat)	F344 rats (Female)	~10-100 ppm As(III) in diet (5 weeks) (NOEL: 1-10 ppm; significant at ≤ 50 ppm)	(Suzuki et al., 2010)
Tissue regeneration/ Hyperplasia (*continued)*	Mild-moderate hyperplasia, *greater severity in KO strain, but NOEL of 1 ppm in both strains;	Urothelium (Mouse)	WT and As3mt KO mice (Female)	50 ppm As(III) in drinking water (6 days); or 10-25 ppm As(III) in drinking water (4 wks)	(Yokohira et al., 2011)
	Mild to moderate bladder hyperplasia (cancer bioassay)	Urinary bladder (Rat)	F344 rats	40 or 100 ppm DMA(V) in feed (2 yrs)	(Arnold et al., 2006)
	Urinary bladder hyperplasia *observed at all exposure levels in males; only observed in lowest exposure group in females	Urinary bladder (Mouse)	CD-1 mice	6, 12, 24 ppm sodium arsenite (2 weeks prior to parental mating through 2 years in adulthood)	(Tokar et al., 2011)
	Urothelial hyperplasia *increased severity & incidence over time	Bladder epithelium (Rat)	F344 rats (Female)	100 ppm As(III) in drinking water (24 hr-14 days)	(Arnold et al., 2013)
Hyperplasia and Metaplasia	Urothelial hyperplasia, occasional metaplasia	Urinary Bladder (Mouse)	C57/BL-6 mice (Female)	0.01% sodium arsenite in drinking water (4 wks)	(Simeonova et al., 2000)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Individual Responses					
Tumor development (animals)	Urothelial cell papillomas *statistically significant positive trend if combine male & female Urothelial cell carcinomas *statistically significant positive trend in females if male & female data combined (low incidence in males precludes statistical analysis	Urinary Bladder (Rat)	F344 rats	2-100 ppm DMA(V) in feed (2 yrs)	(Arnold et al., 2006)
	No increase in tumor incidence	Urinary Bladder (Mouse)	B6C3F1 mice	8, 40, 200, or 500 ppm DMA(V) in feed (2 yrs)	(Arnold et al., 2006)
Tumor development (animals) (continued)	dose-related ↑ in: hepatocellular carcinomas, adrenal tumors (male offspring); lung carcinomas, ovarian tumors, proliferative lesions of oviduct and uterus (female offspring)	Multiple Tissues (Mouse)	C3H mice	42.5, 85 ppm sodium arsenite in drinking water (gestation days 8-18)	(Waalkes et al., 2004b; Waalkes et al., 2003)
	Increased tumor incidence of liver, lung, gall bladder, adrenal gland kidney (male offspring); Liver, lung, ovary, uterus (female offspring)	Multiple Tissues (Mouse)	CD-1 mice	6, 12, 24 ppm sodium arsenite (2 weeks prior parental to mating through2 yrs in adulthood)	(Tokar et al., 2011)
Susceptible Individuals					
Reduced As methylation capacity	Subjects with lower secondary methylation indices had higher risk of skin and bladder cancer	Skin Urinary bladder (Human)	Human Population	Cumulative inorganic arsenic intake 0-20 mg/L-year	(Chen et al., 2003b; Chen et al., 2003a)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Cytotoxicity, regenerative proliferation associated with urinary calculi	Observations of mild cytotoxicity, regenerative proliferation after exposure to calculi-inducing substances	Urinary bladder (Human)	Animals and human population	Drugs (humans) and wax implants (animals)	(Cohen, 2002)
UV-exposure	↑UV-induced DNA strand breaks ↓ UV-induced DNA repair enzyme activity	Skin (Human)	HaCat cells	1 µM sodium arsenite (24 hr) 2 µM sodium arsenite (24 hr)	(Qin et al., 2008)
Human Population Responses					
Inorganic arsenic-associated cancer risk (bladder, lung, skin)	Elevated risks of bladder, lung, and skin cancer in chronically inorganic arsenic-exposed populations (multiple epidemiological studies); primarily limited to populations with water As levels >100 µg/L; limited data suggest urinary inorganic arsenic at levels found to be cytotoxic in rodents are associated with elevated risks. Liver, prostate cancer risk associated with inorganic arsenic (smaller number of studies)	Multiple tissues (Human)	Humans	Wide range of exposure levels and durations	Reviewed in: (Cohen et al., 2013), (Gibb et al., 2011), (Schoen et al., 2004), (NRC, 1999)

[a]Exposure duration abbreviations: minutes (min), hours (hr), days (d), weeks (wks), years (yr)

10.2Preliminary Data on Effects Mediated By Endocrine Signaling

Relevant Health Effects: Developmental Neurotoxicity, Male Infertility, Prostate Cancer

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Molecular Initiating Events					
Interaction with hormone binding domain in hormone receptors	↑reporter activity of ERα hormone binding domain *inhibited by antiestrogen	Kidney (Monkey)	COS-1 cells	1 µM sodium arsenite (24 hr)	(Barr et al., 2009; Rosenblatt and Burnstein, 2009; Stoica et al., 2000)
Modulate signaling pathways (e.g., mitogen activated protein kinases [MAPKs, extracellular signal-regulated kinases [ERK1/2]) responsible for posttranslational modification of coactivators or steroid hormone receptors	Hypothesis	Not applicable (N/A)	N/A	N/A	(Barr et al., 2009; Rosenblatt and Burnstein, 2009)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Modulate histone modifying proteins (e.g., acetylases, methylases) responsible for posttranslational modification of coactivators or steroid hormone receptors	Hypothesis	N/A	N/A	N/A	(Barr et al., 2009; Rosenblatt and Burnstein, 2009)
Biochemical Responses					
Alterations in Nuclear Hormone Receptor Mediated Gene Activation					
Androgen Receptor (AR)					
↓AR amino and carboxyl (N-C) termini interaction	↓luciferase activity in mammalian two-hybrid assay	Prostate (Human)	PC3 cells (human prostate cancer cells)	5 µM arsenic trioxide (ATO) (24 hr)	(Rosenblatt and Burnstein, 2009)
↓AR coactivator-stimulated N-C interaction	↓luciferase activity in mammalian two-hybrid assay	Prostate (Human)	PC3 cells (human prostate cancer cells)	5 µM ATO (24 hr)	(Rosenblatt and Burnstein, 2009)
↓AR coactivator recruitment to chromatin	↓ immuno-precipitation of TIF2 at Prostate-Specific Antigen (PSA) promoter	Prostate (Human)	LNCaP cells (human prostate cancer cells)	5 µM ATO (24 hr)	(Rosenblatt and Burnstein, 2009)
↓AR recruitment to chromatin	↓chromatin immuno-precipitation of AR at PSA promoter	Prostate (Human)	LNCaP cells	5 µM ATO (24 hr)	(Rosenblatt and Burnstein, 2009)
↓AR-mediated gene activation	↓ androgen response element luciferase activity (ARE or PSA)	Prostate (Human)	PC3, LNCaP, or LAPC4 cells (human prostate cancer cells)	1-5 µM ATO (48 hr)	(Rosenblatt and Burnstein, 2009)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
	↓androgen response element luciferase activity	Testes (Mice)	TM4 mouse Sertoli cells	2 µM ATO (48 hr)	(Rosenblatt and Burnstein, 2009)
	↓PSA mRNA	Prostate (Human)	LNCaP cells	2 µM ATO (48 hr)	(Rosenblatt and Burnstein, 2009)
Estrogen Receptor (ER)					
Inhibition of estradiol binding to ERα	↓[3H]estradiol binding *not seen in work by Chow et al., Chow et al. (2004) using ERα competitive screening kit	Breast (Human)	Human breast cancer MCF-7 cells	Ki: 0.5nM sodium arsenite (18 hr)	(Stoica et al., 2000)
	No ↓[3H]estradiol binding	Breast (Human)	Biochemical assay (screening kit)	100-200 nM ATO (not specified)	(Chow et al., 2004)
↑ERα activation	↑estrogen response element reporter construct activity in ERα	Kidney (Monkey)	COS-1 cells	1 nm-10 µM sodium arsenite (24 hr)	(Stoica et al., 2000)
Altered ER-mediated gene activation	↓vitellogenin expression (mRNA)	Liver (Chicken)	Chick Embryo	10 – 50 µmol/kg As(III) (4 hr) 10 µmol/kg E2 (3 hr)	(Davey et al., 2007)
	↓Estrogen Response Element expression (luciferase expression or mRNA)	Breast (Human)	Human breast cancer MCF-7 cells	2.5 µM As(III) (EC50) (24 hr)	(Davey et al., 2007)
	↓GREB1 basal (mRNA)	Breast (Human)	Human breast cancer MCF-7 cells	5 µM As(III) (EC50) (24 hr)	(Davey et al., 2007)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
	↓GREB1-E2 induced (mRNA)	Breast (Human)	Human breast cancer MCF-7 cells	5 µM As(III) (EC50) (24 hr)	(Davey et al., 2007)
	↓ERα basal (mRNA)	Breast (Human)	Human breast cancer MCF-7 cells	5 µM As(III) (EC50) (24 hr)	(Davey et al., 2007; Stoica et al., 2000)
Altered ER-mediated gene activation (continued)	↓ERα basal (mRNA	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO (24 or 48 hr)	(Chow et al., 2004)
	↓ERα hormone induced (mRNA) *synergistic ↓ with E2	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO + 10 nM estradiol (24 or 48 hr)	(Chow et al., 2004)
	↓Estrogen Response Element expression (luciferase expression)	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO (24 or 48 hr) 2 µM ATO + 10 nM estradiol (24 or 48 hr)	(Chow et al., 2004)
	↓c-myc protein ↓c-myc protein induced by E2	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO (48 hr) 2 µM ATO + 10 nM estradiol (48 hr)	(Chow et al., 2004)
	↑pS2 (mRNA) *↑blocked by antiestrogen	Breast (Human)	Human breast cancer MCF-7 cells	1µM sodium arsenite (24 hr)	(Stoica et al., 2000)
↓ER-mediated protein levels	↓ERα protein	Breast (Human)	Human breast cancer MCF-7 cells	0.1, 1, or 5 µM sodium arsenite (24 hr)	(Stoica et al., 2000)
	↓ERα protein ↓ERα hormone induced protein *synergistic ↓ with E2	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO (48 hr) 2 µM ATO + 10 nM 17β-estradiol (48 hr)	(Chow et al., 2004)
	↑progesterone receptor protein *↑blocked by antiestrogen	Breast (Human)	Human breast cancer MCF-7 cells	1 µM sodium arsenite (24 hr)	(Stoica et al., 2000)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
	↓Vascular Endothelial Growth Factor protein (mRNA and protein)	Uterus (Rat)	Sprague-Dawley rats (Female)	4 µg/ml sodium arsenite (28 days)	(Chatterjee and Chatterji, 2010)
Glucocorticoid Receptor (GR)					
Altered histone post-translational co-activator protein activity at GR-regulated promoter	↓protein methyltransferase (CARM1) / coactivator (GRIP1) interaction	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	8 µM sodium arsenite + 5 nM dexamethasone (Dex) (30 min)	(Barr et al., 2009)
Altered histone post-translational modifications at GR-regulated promoter	↓ acetylation (H3K18ac) ↓methylation (H3R17me)	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	8 µM sodium arsenite + 5 nM Dex (15 min)	(Barr et al., 2009)
↓chromatin remodeling at GR regulated promoter	↓A Sac1 endonuclease cleavage site access	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	8 µM sodium arsenite + 5 nM Dex (30 and 60 min)	(Barr et al., 2009)
↓GR binding to glucocorticoid response elements (GREs)	↓GR binding to GREs in H-Ras and Raf-1 promoters (chromatin immuno-precipitation) *no ↓binding in vitro	Developing Brain (Mouse)	C57BL/6 mice	50 ppb sodium arsenite (2 weeks prior to gestation + through weaning)	(Martinez-Finley et al., 2011)
↓ transcription initiation at GR-regulated promoter	↓reporter gene mRNA initiation	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	8 µM sodium arsenite + 5 nM Dex (120 min)	(Barr et al., 2009)
	↓endogenous GR-regulated mRNA (serum glucocorticoid kinase [SGK]) initiation	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	8 µM sodium arsenite + 5 nM Dex (120 min)	(Barr et al., 2009)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
↑/↓GR mediated gene transcription	↓reporter gene activity (MMTV-chloramphenicol acetyl transferase [MMTV-CAT])	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	0.5-8 µM sodium arsenite + 100 nM Dex (4 hr)	(Barr et al., 2009)
	↑ reporter gene activity (G2T-luciferase construct) ↓ reporter gene activity (G2T-luciferase construct)	Liver (Rat)	EDR3 cells (hepatoma cell line)	<1 µM sodium arsenite + 50 nM Dex (18 hr) ≤ 1-3 µM sodium arsenite + 50 nM Dex (18 hr)	(Bodwell et al., 2006)
Mineralocorticoid Receptor (MR)					
↑/↓MR-mediated gene transcription	↑ reporter gene activity (G2T-luciferase construct) ↓ reporter gene activity (G2T-luciferase construct)	Liver (Rat)	EDR3 cells (hepatoma cell line)	<1 µM sodium arsenite + 0.5 nM aldosterone (18 hr) ≤ 1-3 µM sodium arsenite + 0.5 nM aldosterone (18 hr)	(Bodwell et al., 2006)
Progesterone Receptor (PR)					
↑/↓PR-mediated gene transcription	↑ reporter gene activity (G2T-luciferase construct) ↓ reporter gene activity (G2T-luciferase construct)	Liver (Rat)	EDR3 cells (hepatoma cell line)	<1 µM sodium arsenite + 50 nM progesterone (18 hr) ≤ 1-3 µM sodium arsenite + 50 nM progesterone (18 hr)	(Bodwell et al., 2006)
Thyroid Hormone Receptor (TR)					

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Altered TR gene induction	↓TR response element-luciferase (TRE-luc)	Pituitary (Rat)	GH3 rat pituitary tumor cells	0.5-2 µM As(III) + 2 nM Thyroid Hormone (T3) (24 hr)	(Davey et al., 2008)
	↑DIO1 ↓DIO1 ↑DIO1	Pituitary (Rat)	GH3 rat pituitary tumor cells	0.1-1 µM As(III) + 2 nM T3 (6 hr) 2 µM As(III) + 2 nM T3 (6 hr) 1-2 µM As(III) +2 nM T3 (24 hr)	(Davey et al., 2008)
Retinoic acid Receptor (RAR)					
Altered RAR-mediated gene activation	↑Retinoic acid inducible RAR response element(RARE)-luciferase expression induced by all trans-retinoic acid (ATRA)	Embryo (Human)	NTERA-2 (N2) human embryonic carcinoma cells	0.05-0.025 µM As(III) (24 hr)	(Davey et al., 2008)
	↓RARE-luciferase expression induced by ATRA	Embryo (Human)	N2 cells	2.0 µM As(III) (24 hr)	(Davey et al., 2008)
	↑CYP26A induced by ATRA ↓ CYP26A induced by ATRA	Embryo (Human)	N2 cells	0.01 µM As(III) (24 hr) ≤ 0.025 µM As(III) (24 hr)	(Davey et al., 2008)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Alterations in Cell Signaling Pathways Mediated by Hormone Receptors					
Mitogen-activated protein kinase (MAPK) pathway alterations	↓H-Ras & Raf-1 mRNA *no ↓ in protein	Developing Brain (Mouse)	C57BL/6 mice (Postnatal day 35)	50 ppb sodium arsenite (2 weeks prior to gestation + through weaning on postnatal day [PND] 23)	(Martinez-Finley et al., 2011)
	↓phosphorylated-ERK	Developing Brain (hypothalamus; Mouse)	C57BL/6 mice (Postnatal day 35)	50 ppb sodium arsenite (2 weeks prior to gestation + through weaning on PND 23)	(Martinez-Finley et al., 2011)
Cellular Responses					
Cytotoxicity	↓colony forming ability	Breast (Human)	Human breast cancer MCF-7 cells	15 µM As(III) (LC50) (24 hr); or 25 µM As(III) (LC50) + 50 pM E2 (24 hr)	(Davey et al., 2007)
			Human breast cancer MCF-7 cells	2 µM ATO + 10 nM 17β-estradiol (IC50) (72 hr) *reduced viability as compared to E2 alone	(Chow et al., 2004)
Cytotoxicity (continued)	↓colony forming ability (continued)	Breast (Human) (continued)	Human breast cancer MCF-7 cells	8 µM ATO (IC50) (24 hr) 1-2 µM ATO (IC50) (72 hr)	(Chow et al., 2004)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
			Human breast cancer MDA-MB-231 cells	17 µM ATO (IC50) (24 hr) 4-8 µM ATO (IC50) (72 hr)	(Chow et al., 2004)
		Embryo	NTERA-2 (N2) human embryonic carcinoma cells	3 µM As(III) (LC50) (24 hr)	(Davey et al., 2008)
		Pituitary (Rat)	GH3 rat pituitary tumor cells	5-10 µM As(III) (LC50) (24 hr)	(Davey et al., 2008)
Proliferation	↑colony forming ability	Pituitary (Rat)	GH3 rat pituitary tumor cells	0.01-1 µM As(III) + 10 nM thyroid hormone (T3) (24 hr)	(Davey et al., 2008)
	↑cell number *growth inhibited by antiestrogen	Breast (Human)	Human breast cancer MCF-7 cells	1 µM sodium arsenite (5 - 8 days)	(Stoica et al., 2000)
	↓cell number	Prostate (Human)	LNCaP, or LAPCaP-R1 cells (human prostate cancer cells)	5 µM ATO (3 days and 5 days)	(Rosenblatt and Burnstein, 2009)
Altered cell cycle	21%↓ G1 phase cells 8%↓ S phase cells 12%↓ G2/M phase cells	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO (48 hr; greater effect at 72 hr)	(Chow et al., 2004)
	26%↑ G1 phase cells 8%↓ S phase cells 10%↓ G2/M phase cells	Breast (Human)	Human breast cancer MCF-7 cells	2 µM ATO + 10 nM 17β-estradiol (48 hr) *reduced viability as compared to	(Chow et al., 2004)
	↓G1 cell cycle proteins (cyclin D1 and CDK4) mRNA	Uterus (Rat)	Sprague-Dawley rats (Female)	4 µg/ml sodium arsenite (28 days)	(Chatterjee and Chatterji, 2010)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Altered hormone receptor distribution	No change in cytosolic MR protein ↓nuclear MR protein	Developing Brain (Hippo-campus) (Mouse)	C57BL/6 mice (PND 35-40)	55 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez-Finley et al., 2009)
	↓ cytosolic GR protein ↓nuclear GR protein	Developing Brain (Hippo-campus) (Mouse)	C57BL/6 mice (PND 35-40)	55 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez-Finley et al., 2009)
	↓ cytosolic GR protein ↑nuclear GR protein	Developing Brain (hypothalamus; Mouse)	C57BL/6 mice (PND 31-40)	50 ppb sodium arsenate (2 weeks prior to gestation through weaning on PND 21)	(Goggin et al., 2012)
Tissue or Organ System Responses					
Altered hypothalamic-pituitary-adrenal (HPA) axis activity	↑corticotrophin releasing factor	Developing Brain (hypo-thalamus; Mouse)	C57BL/6 mice (PND 31-40)	50 ppb sodium arsenate (2 weeks prior to gestation through weaning on PND 21)	(Goggin et al., 2012)
	↑base-line corticosterone (CORT)	Plasma (Mouse)	C57BL/6 mice (PND 35)	50 ppb sodium arsenate (2 weeks prior to gestation through weaning on PND 21 or 23)	(Goggin et al., 2012)
			C57BL/6 mice (PND 75-90)		(Martinez et al., 2008)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
	↑plasma corticosterone	Plasma (Rat)	Albino rats (Male)	5 mg/kg/day sodium arsenite (6 days/wk for 4 wks)	(Jana et al., 2006)
Altered hypothalamic-pituitary-gonadal (HPG) axis activity	Dose dependent ↓ in: plasma hormone levels (luteinizing hormone [LH], follicle-stimulating hormone [FSH], testosterone;	Plasma (Rat)	Wistar rats (Male)	5 or 6 mg/kg/day sodium arsenite (26 days)	(Sarkar et al., 2003)
	↓in plasma LH, FSH, testosterone	Plasma (Rat)	Albino rats (Male)	5 mg/kg/day sodium arsenite (6 days/wk for 4 wks)	(Jana et al., 2006)
Altered hypothalamic-pituitary-gonadal (HPG) axis activity (continued)	↓serum estradiol levels	Serum (Rat)	Sprague-Dawley rats (Female)	0.4, 4, 40 or 80 µg/ml sodium arsenite (14 -56 days)	(Chatterjee and Chatterji, 2010)
	↓ serum LH, FSH levels	Serum (Rat)	Sprague-Dawley rats (Female)	4 µg/ml sodium arsenite (28 days)	(Chatterjee and Chatterji, 2010)
	↓ plasma estradiol, LH, FSH levels *No effects detected at 16 days of exposure	Plasma (Rat)	Sprague-Dawley rats (Female)	0.4 ppm sodium arsenite (16 or 28 days)	(Chattopadhyay et al., 1999)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Testicular toxicity	↓in: paired testicular weights; and testicular testosterone; Altered testicular enzyme levels; germ cell degeneration at stage VII *Effects alleviated by co-administration of human chorionic gonadotrophin **Effects enhanced by co-administration of oestradiol	Male reproductive organs (Rat)	Albino rats (Male)	5 mg/kg/day sodium arsenite (6 days/wk for 4 wks)	(Jana et al., 2006)
	↓ testicular weights, sperm count and motility, altered testicular enzyme activities	Male reproductive organs (Mouse)	Swiss albino mice (Male)	53.39 µmol/L sodium arsenite (365 days)	(Pant et al., 2004)
Impaired Spermatogenesis	Dose dependent ↓ in: reproductive organ weight; epididymal sperm count; and degeneration of germ cells at stage VII	Male reproductive organs (Rat)	Wistar rats (Male)	5 or 6 mg/kg/day sodium arsenite (26 days)	(Sarkar et al., 2003)
Female reproductive toxicity	↓uterine weight; altered uterine morphology	Female reproductive organs (Rat)	Sprague-Dawley rats (Female)	4 µg/ml sodium arsenite (28 days)	(Chatterjee and Chatterji, 2010)
	↓uterine, ovary and vagina weights, ovarian enzymes *No effects detected at 16 days of exposure	Female reproductive organs (Rat)	Sprague-Dawley rats (Female)	0.4 ppm sodium arsenite (16 or 28 days)	(Chattopadhyay et al., 1999)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Altered protein glycosylation	↓fully glycosylated 11β-Hydroxysteroid Dehydrogenase Type 1	Developing Brain (hippo-campus; Mouse)	C57BL/6 mice (PND 75- 90)	50 ppb sodium arsenate (2 weeks prior to gestation through weaning on PND 21)	(Goggin et al., 2012)
Altered receptor levels	↑(trend) GR mRNA	Adolescent Brain (hippo-campus; Mouse)	C57BL/6 mice (PND 31-40)	50 ppb sodium arsenate (2 weeks prior to gestation through weaning on PND 21)	(Goggin et al., 2012)
	↓corticotrophin -releasing factor receptor	Adult Brain (hippocampus ; Mouse)	C57BL/6 mice (PND 75 - 90)	50 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez et al., 2008)
	↓estrogen receptor mRNA and protein	Uterus (Rat)	Sprague-Dawley rats (Female)	4 µg/ml sodium arsenite (28 days)	(Chatterjee and Chatterji, 2010)
Altered receptor sensitivity	↑specific binding to serotonin receptor (5HT-1A)	Adult Brain (hippo-campus; Mouse)	C57BL/6 mice (PND 75 - 90)	50 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez et al., 2008)
Altered neurotransmitter levels	↑ dopamine ↓ noradrenaline ↓5-HT	Adult Brain (hypothalamus, pituitary; rat)	Albino rats (Male)	5 mg/kg/day sodium arsenite (6 days/wk for 4 wks)	(Jana et al., 2006)
Impaired morphogenesis	↓T3-dependent tail fin resorption	Tail (Xenopus laevis)	Ex-vivo (Xenopus laevis tails)	0.05-4 µM As(III) + 10 nM T3 (4 days)	(Davey et al., 2008)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Individual Response					
Impaired spatial learning and memory	Novel Object Test ↑time to recognize presence of novel object ↓entries in presence of novel object 8-way Radial Arm Maze ↑entry errors	Mouse	C57BL/6 mice (PND 35-40)	55 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez-Finley et al., 2009)
Altered stress response	↑base-line corticosterone (CORT) Blunted CORT increase following stressor	Plasma (Mouse)	C57BL/6 mice (PND 35)	50 ppb sodium arsenate (2 weeks prior to gestation through weaning on PND 21)	(Goggin et al., 2012)
Depressive like behavior	Learned Helplessness Task ↑latency to escape in	Mouse	C57BL/6 mice (PND 75 - 90)	50 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez et al., 2008)
	Forced Swim Test ↑immobility	Mouse	C57BL/6 mice (PND 75 - 90)	50 ppb sodium arsenate (2 weeks prior to gestation through PND 23)	(Martinez et al., 2008)

Key Events	Observations	Organ System	Test System	Dose (Exposure Duration)[a]	References
Susceptible Individuals					
Developing children	Indicators of developmental neurotoxicity in rodents coupled with lower cogitative performance in epidemiology studies	See rows above and below for animal and epidemiologic al data, respectively	Rats or human population	Varies	(Goggin et al., 2012; Martinez-Finley et al., 2009; Martinez et al., 2008; Wasserman et al., 2007)
Population Level Response					
Developmental neurotoxicity	↓performance on Wechsler Preschool & Primary Scale of Intelligence	Brain (Human)	6-year-old children (Araihazar, Bangladesh)	Mean 120.1 µg/L in urine (not specified)	(Wasserman et al., 2007)
Male infertility	Abnormal sperm, ↓ sperm count, sperm mobility	(Human & animal model)	Human and animal models	Varies	(Rosenblatt and Burnstein, 2009)
	↑ male infertility	Reproductive system (Human)	Human population	Varies	(Shen et al., 2013)
Prostate Cancer	↑prostate cancer mortality associated with inorganic arsenic exposures	Prostate (Human)	Human population	Varies	Reviewed in (Prins, 2008)

[a]Exposure duration abbreviations: minutes (min), hours (hr), days (d), weeks (wks), years (yr)

10.3Preliminary Data on Effects Mediated by Epigenetic Mechanisms

Relevant Health Effects: Bladder cancer, skin cancer, skin lesions

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
Molecular Initiating Events					
↓S-adenosyl-methionine (SAM)	SAM depletion associated with methylation, reduction of inorganic arsenic species	Multiple	Multiple	Multiple	Reviewed in (Reichard and Puga, 2010), (Martínez et al., 2011),(Ren et al., 2011)
↓SAM unrelated to inorganic arsenic methylation	↓SAM in cells with low capacity to methylate inorganic arsenic; ↑expression of transsulfuration enzymes in glutathione (GSH) synthesis	Prostate (Human)	Transformed prostate epithelial cell line (RPWE-1)	5 µM arsenite (16 wks)	Coppin et al., 2008 Reviewed in (Reichard and Puga, 2010)
↑oxidative stress and subsequent GSH depletion	↑reactive oxygen species (ROS); ↑oxidation of GSH	Multiple	Multiple	Multiple	Reviewed in (Reichard and Puga, 2010)
	transformation of HELF cells via ↑ROS ->ERK/NFKB activation ->hsa-miR-21 upregulation	Embryonic lung (Human)	Embryonic lung fibroblasts (HELF)	1 µM sodium arsenite (up to 30 cell passages)	(Ling et al., 2012)
Biochemical Responses					
Altered DNA methyltransferases (DNMTs) activity	↓ DNMT activity (no change in DNMT mRNA expression), associated with hypomethylation	Prostate (Human)	Human prostate epithelial cells (RWPE-1)	5 µM As(III) (29 weeks)	(Benbrahim-Tallaa et al., 2005)
	SAM depletion, ↓ expression of DNMT1 and DNMT3, global hypomethylation	Skin (Human)	Human HaCat keratinocytes	up to 5 µM As(III) (3 days)	(Reichard et al., 2007)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
Global DNA methylation changes	Hypermethylation only in folate adequate individuals	Blood (Human)	Peripheral blood lymphocyte (PBL) DNA	2-250 µg/L As(III) (>4 yrs)	(Pilsner et al., 2007)
	Hypermethylation	Blood (Human)	PBL DNA	250-500 µg/L As(III) (>6 months, mean = 10 yrs)	(Majumdar et al., 2010)
	Hypomethylation	Skin/Blood (Human)	PBL DNA in individuals with skin lesions	2-250 µg/L (As[III]) (>2 yrs)	(Pilsner et al., 2009)
Global DNA methylation changes (*continued*)	hypomethylation, increased GSH and decreased SAM levels	Prostate (Human)	Human prostate epithelial cells (RWPE-1)	5 µM As(III) (16 wks)	(Coppin et al., 2008)
	hypomethylation, decreased DNMT activity with no change in DNMT mRNA expression	Prostate (Human)	Human prostate epithelial cells (RWPE-1)	5 µM As(III) (29 wks)	(Benbrahim-Tallaa et al., 2005)
	hypomethylation	Skin (Human)	HaCaT keratinocytes	0.2 µM (4 wks)	(Reichard et al., 2007)
	hypomethylation	Liver (Rat)	Rat liver epithelial cells (TRL 1215)	125-500 nM As(III) (18 wks)	(Zhao et al., 1997)
	hypomethylation (after 1 day) and chromosomal instability (8 weeks)	Lung (Hamster)	Chinese hamster cells (V79-Cl3)	10 µM As(III) (1 day - 8 wks)	(Sciandrello et al., 2004)
	hypomethylation, increased expression of ERα and cyclin CD1 mRNA and protein	Liver (Mouse)	129/SvJ mice	45 ppm As(III) (48 wks)	(Chen et al., 2004b)
	hypomethylation, gene expression changes	Liver (Mouse)	Homozygous Tg.AC mice	150 ppm As(III); 200 ppm As(V); 1500 ppm MMA(V); or 1200 ppm DMA(V) (17 wks)	(Xie et al., 2004)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	hypomethylation; correlation with c-myc gene expression, tumor formation in nude mice	Liver (Rat)	Rat liver epithelial cells (TRL 1215)	125-500 nM As(III) (18 wks)	(Chen et al., 2001)
	hypo and hypermethylation	Kidney and lung (Human)	kidney (UOK) and lung epithelial type II (A549) cell lines	As(III) (various)	(Zhong and Mass, 2001)
	Altered methylation patterns in repetitive DNA elements (high in Alu and low in LINE-1 with higher inorganic arsenic exposure)	Blood (Human)	elderly men; blood leukocyte DNA methylation	0.02-1.45 µg/g toenail arsenic (unspecified)[b]	(Lambrou et al., 2012)
Global DNA methylation changes (*continued*)	↑Global methylation	Brain cortex and hippocampus (Rat)	Wistar Rats	3 ppm sodium arsenite; or 36 ppm sodium arsenite (10 days prior to gestation through 1 month postnatal development)	(Martínez et al., 2011)
	Hypomethylation	Brain cortex (Rat)	Wistar Rats	3 ppm sodium arsenite; or 36 ppm sodium arsenite (10 days prior to gestation through 3 or 4 months postnatal development)	(Martínez et al., 2011)
Gene specific methylation changes	182 hypermethylated genes (17 = tumor suppressor); 1 hypomethylated gene	Skin and Blood (Human)	PBL DNA (Zimapan, Mexico)	110 µg As/L (mean) (>2 yrs)	(Smeester et al., 2011)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	Aberrant DNA methylation; cellular transformation	Bladder (Human)	Human bladder cell line (UROtsa)	50 nM MMA(III) (12, 24 wks)	(Wnek et al., 2010)
	altered DNA methylation of 455 promoters (primarily hypomethylation), associated with urinary iAs	Urine and blood (Human)	Human Urine (16 females in Zimapan, Hildago, Mexico)	3.6-31.8 ng Total As/mL in urine (10.7 ng/mL [mean]) (unspecified)	(Bailey et al., 2013)
	DAPK promoter hypermethylation	Bladder (Human)	Human bladder, kidney, ureter tumors from urothelial carcinoma patients (Southwest Taiwan)	Unspecified high doses from well water (unspecified)	(Chen et al., 2007a)
	p53, p16 promoter hypermethylation (dose-dependent), hypomethylation in highest exposure group	Blood (Human) associated with skin lesions	Human PBL (West Bengal, India)	>50 µg/L As in drinking water (≤ 6 months) highest group: 300-1000 As µg/L in drinking water (≤ 6 months)	(Chanda et al., 2006)
Gene specific methylation changes (*continued*)	p16 promoter hypermethylation	Blood (Human)	Human PBL in patients with arseniasis (Guizhou Province, China)	Unspecified doses from use of unventilated coal stove with high As (unspecified)	(Zhang et al., 2007)
	RASSF1A, PRSS3 promoter hypermethylation	Bladder (Human)	Human Bladder tumors (New Hampshire, U.S.)	>0.26 µg/g toenail As (unspecified)	(Marsit et al., 2006b)
	DBC1, FAM83A, ZSCAN12, C1QTNF6 promoter hypermethylation	Bladder (Human)	UROtsa urothelial cells	1 µM As(III), or 50 nM MMA(III) (52 wks)	(Jensen et al., 2008)
	WNT5A promoter hypermethylation	Bladder (Human)	UROtsa urothelial cells	1 µM As(III), or 50 nM MMA(III) (52 wks)	(Jensen et al., 2009b)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	DAPK promoter hypermethylation and reduced expression	Bladder (Human)	Uroepithelial cells (SV-HUC-1)	2,4,10 µM As(III) (2 days)	(Chai et al., 2007)
	p16 promoter hypermethylation	Immune System (Human)	Myeloma cells (U266)	1,2 µM As_2O_3 (3 days)	(Fu and Shen, 2005)
	p53 promoter hypermethylation	Lung (Human)	Lung adenocarcinoma cells (A549)	0.8-2 µM As(III), or 30-300 µM As(V) (1 wk)	(Mass and Wang, 1997)
	c-myc, c-Ha-ras promoter hypomethylation	Embryo (Hamster)	Syrian hamster embryo cells	3-10 µM As(III), or 50-150 µM As(V) (2 ds)	(Takahashi et al., 2002)
	p16, RASSF1 promoter hypermethylation, ↓ expression of p16 and RASSF1, increased occurrence of lung adenocarcinoma	Lung (Mouse)	A/J mice	1, 10, 100 ppm As(V) (18 months)	(Cui et al., 2006a)
	p16, RASSF1A, E-cadherin, GSTP1 promoter hypomethylation	Liver (Human)	HepG2 and Huh-7 liver cells	2-10 µM As(III) (3 days)	(Cui et al., 2006b)
	c-Ha-ras promoter hypomethylation in dietary methyl deficient mice, steatosis and microgranulomas	Liver (Mouse)	C57BL/6J mice	2.6-14.6 µg As(III)/g body weight/day (18.5 wks)	(Okoji et al., 2002)
Gene specific methylation changes (*continued*)	ERα promoter hypomethylation	Liver (Mouse)	C3H mice (Adult male with hepatocellular carcinoma [HCC] after only in utero exposure)	85 ppm As(III) (gestational day [GD] 8 – 18)	(Waalkes et al., 2004a)
	ERα promoter hypomethylation, ↑ expression of ERα and cyclin CD1 mRNA and protein	Liver (Mouse)	129/SvJ mice	45 ppm As(III) (48 wks)	(Chen et al., 2004b)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	hyper- and hypomethylation of VHL promoter	Kidney (Human)	Human kidney cells (UOK123, UOK109, UOK121)	IC_{30}, IC_{50}, or IC_{80} of each cell line: 7 – 93 µM As(III) (4 wks)	(Zhong and Mass, 2001)
Histone modification	↓ acetylation (H3K18ac) ↓methylation (H3R17me)	Tumor (Mouse)	1470.2 cells (mouse adenocarcinoma derived)	8 µM sodium arsenite + 5 nM Dex (15 min)	(Barr et al., 2009)
	↑ histone acetylation (H3; lysine 14) and phosphorylation (H3; serine 10) at c-jun and c-fos chromatin, increased expression of c-jun and c-fos	Lung (Human)	Human fibroblasts (WI-38 cells)	400 µM As(III), (up to 1 hr)	(Li et al., 2003)
	↑ histone H3acetylation (H3K9); inhibition of HDAC activity	Liver (Human)	Human hepatoma HepG2 cells	5-10 µM As(III) (1 day)	(Ramirez et al., 2008)
	↓ histone acetylation: H4K16, H3K9, K14, K18, K23	Bladder (Human)	Human uroepithelial cells (UROtsa)	1-10 µM As(III) or 0.3-3 µM MMA(III) (up to 1 day)	(Chu et al., 2011)
	↓ H4; lysine 16 acetylation	Bladder (Human)	Human bladder epithelial cells (UROtsa)	150 µM As(III), or 300 µM MMA(III) (1 day)	(Jo et al., 2009)
	↓ H3 acetylation of FAM83A, DCB1, ZSCAN12, KRT7, C1QTNF6, FGF5; increased acetylation of KCNK10, NEFL	Bladder (Human)	UROtsa and URO-ASSC urothelial cells	1 µM As(III), or 50 nM MMA(III) (52 wks)	(Jensen et al., 2008)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
Histone modification (*continued)*	↑permissive transcription histone modifications (DiMeK4; AcH3) ↓repressive transcription histone modifications (TriMeK27, DiMeK9)	Bladder (Human)	UROtsa and URO-ASSC urothelial cells	1 µM As(III), or 50 nM MMA(III) (52 wks)	(Jensen et al., 2009b)
	↓ H3K27 trimethylation, ↑ H3K9 dimethylation and H3K4 trimethylation (increase in HMT G9a protein and mRNA levels)	Lung (Human)	A549 human lung adenocarcinoma cells	0.1-10 µM As(III) (1 day)	(Zhou et al., 2008)
	↑ H3K4 trimethylation, maintained after inorganic arsenic removal = inherited through cell division	Lung (Human)	A549 human lung adenocarcinoma cells	0.1-1 µM As(III) (1 or 7 days)	(Zhou et al., 2009)
	↑ H2AX phosphorylation	Skin (Human)	Melanoma cells (RPMI7591)	1, 2.5, or 5 µM As(III) (1 day)	(Zykova et al., 2006)
	↑ H3K9me2 and ↓ H3K9ac with increased urinary inorganic arsenic; other histone marks correlated with water inorganic arsenic in gender specific manner	Blood (Human)	Peripheral blood mononuclear cells (Bangladesh cohort [n=40])	91.5 µg/L urinary inorganic arsenic (median) (unspecified)	(Chervona et al., 2012); (Arita et al., 2012)
	↑ H3K9me2; ↓ p16INK4a expression; no change in promoter DNA methylation	Liver (Mouse)	C57Bl/6J mice	50 ppm sodium arsenite (6 months)	(Suzuki and Nohara, 2013)
Altered MicroRNA expression	Upregulation of hsa-miR-22,34a,221,222 and downregulation of hsa-miR-210	Immune system (Human)	Human immortalized lymphoblast cells (TK6 cell line)	≤ 2 µM As(III) (6 days)	(Marsit et al., 2006a)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	downregulation of miRNA-19a - cell growth arrest and apoptosis	Bladder (Human)	T24 human bladder carcinoma cells	4 µM As_2O_3 (24 hr)	(Cao et al., 2011)
Altered MicroRNA expression (continued)	upregulation of hsa-miR-2909; molecular responses linked to immune response	Immune system (Human)	Peripheral blood mononuclear cells (PBMCs)	2 µM sodium arsenite (48 hr)	(Kaul et al., 2014)
	85 miRNA upregulated, 52 downregulated; predicted to be involved in regulating phosphoproteins and alternative gene splicing	Vascular system (Human)	Umbilical vein endothelial cells (HUVECs)	20 µM sodium arsenite (24 hr)	(Li et al., 2012)
	hsa-miR-21 upregulation	Embryonic, lung (Human)	Embryonic lung fibroblast (HELF)	1 µM sodium arsenite (up 30 cell passages)	(Ling et al., 2012)
Cellular Phenotypic Changes					
Malignant transformation	transformation of HELF cells via increased ROS ->ERK/NFKB activation ->hsa-miR-21 upregulation	Embryonic, lung (Human)	Embryonic lung fibroblast (HELF)	1 µM sodium arsenite (up 30 cell passages)	(Ling et al., 2012)
	transformation of p53 knocked down HBECs; downregulated hsa-miR-200b via promoter methylation	Lung (human)	p53(low) human bronchial epithelial cells	2.5 µM sodium arsenite (16 wks)	(Wang et al., 2011b)
	Altered H3 and H4 acetylation during malignant transformation	Bladder (Human)	UROtsa and URO-ASSC urothelial cells	1 µM As(III), or 50 nM MMA(III) (52 wks)	(Jensen et al., 2008)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	Increase in "permissive" histone modifications AcH3 and DiMeK4; repressive modifications TriMeK27 and DiMeK9 were decreased → non-canonical WNT5A signaling and malignant transformation	Bladder (Human)	UROtsa and URO-ASSC urothelial cells	50 nM MMA(III) (24+ wks)	(Jensen et al., 2009b)
Malignant transformation (continued)	Genome-wide changes in promoter DNA methylation, increasing with duration of exposure, in parallel with phenotypic changes (transformation)	Bladder (Human)	UROtsa and URO-ASSC urothelial cells	1 µM As(III), or 50 nM MMA(III) (up to 52 wks)	(Jensen et al., 2009a)
Tissue/Organ Responses					
Skin Lesions	Development of skin lesions associated with inorganic arsenic exposure and PBL hypomethylation	Skin/Blood (Human)	PBL DNA in individuals with skin lesions (Araihazar, Bangladesh)	121 µg/L urinary As (>2 yrs)	(Pilsner et al., 2009)
	Risk of skin lesions associated with DAPK and p16 hypermethylation	Skin and blood (Human)	PBL DNA in individuals (West Bengal, India)	567.25 µg/L mean urinary As(III) (with lesions) Mean urine As(III) 495.48 µg/L mean urinary As(III) (w/o lesions), 567.25 µg/L (with lesions)	(Banerjee et al., 2013)
Adverse liver effects	Hepatic steatosis with DNA hypomethylation	Liver (Mouse)	129/SvJ mice	45 ppm As(III) (48 wks)	(Chen et al., 2004b)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	Hepatocellular carcinoma	Liver (Mouse)	Adult male C3H mice with HCC after only in utero exposure	85 ppm As(III) (gestational day [GD] 8 – 18)	(Waalkes et al., 2004a)
	Steatosis and microgranulomas with c-Ha-ras promoter hypomethylation in dietary methyl deficient mice	Liver (Mouse)	C57BL/6J mice	2.6-14.6 µg As(III)/g body weight/day (18.5 wks)	(Okoji et al., 2002)
Individual Responses					
Contextual memory deficits	↓freezing behavior *highest dose group: significant at all time points 2 -4 months of age Lowest dose group: significant at 1 time point at 2 months of age; all time points 3 & 4 months of age	Whole animal (Rat)	Wistar Rats	3 or 36 ppm sodium arsenite, (10 days prior to gestation through 1, 2, 3, or 4 months postnatal development)	(Martínez et al., 2011)
Susceptible Individual response					
Diet (e.g., deficiencies in methyl, folate, methionine)	Altered DNA methylation patterns in repetitive Alu and LINE DNA elements (high Alu methylation correlated with high inorganic arsenic exposure in low folate condition, and vice versa) following low levels of environmental exposure	Blood (Human; Elderly men)	Blood leukocyte DNA in human cohort study	0.02-1.45 µg/g toenail arsenic (unspecified)	(Lambrou et al., 2012)
	Hypermethylation, modified by folate	Blood (Human)	PBL DNA	2-250 µg/L As(III) (>4 yrs)	(Pilsner et al., 2007)
	development of skin lesions associated with low folate	Skin/Blood (Human)	PBL DNA in individuals with skin lesions	2-250 µg/L As(III) (>2 yrs)	(Pilsner et al., 2009)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
	c-Ha-ras promoter hypomethylation, steatosis and microgranulomas	Liver (Mouse)	C57BL/6J mice	2.6-14.6 µg iAs (III)/g body weight/day (18.5 weeks)	(Okoji et al., 2002)
	5357 CpG islands altered with high maternal folate + inorganic arsenic	Fetal liver (Mouse)	CD-1 mice (Pregnant females)	85 ppm As(III) (GD 8-18) + High maternal folate intake (11 mg/kg) (GD 5-18)	(Tsang et al., 2012)
Life stage (in utero exposure)	global hypomethylation w/ high exposure, PP1 promoter hypomethylation, reduced fear memory	Brain (rat)	Wistar rats	3 or 36 ppm sodium arsenite (gestation to 4 months postnatal development)	(Martínez et al., 2011)
	ERα promoter hypomethylation, HCC	Liver (Mouse)	C3H mice (Adult; male)	85 ppm As(III) (GD 8 – 18)	(Waalkes et al., 2004a)
	12 miRNAs upregulated (linked to cancer, diabetes and immune response signaling pathways)	Blood (Human)	cord blood (Mexican women's cohort)	0.456-236 µg/L inorganic arsenic in maternal drinking water inorganic arsenic range of 0.456-236 µg/L; maternal urine inorganic arsenic range of 6.2-319.7 µg/L inorganic arsenic in maternal urine (unspecified)	(Rager et al., 2014)
	5357 CpG islands altered with high maternal folate + inorganic arsenic	Fetal liver (Mouse)	CD-1 mice (Pregnant females)	85 ppm As(III) (GD 8-18) + High maternal folate intake (11 mg/kg) for (GD 5-18)	(Tsang et al., 2012)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
Gender	Males: ↓DNA methylation; ↓DNMT1 expression (no change in SAM content) Females: ↑DNA methylation in females (no change in DNMT1 levels) ↓SAM content	liver (Mouse)	C57BL/6J mice	50 ppm sodium arsenite + methyl-deficient diet ad libitum (5 months)	(Nohara et al., 2011)
Genetics	AS3MT haplotype associated with efficient inorganic arsenic metabolism, methylation of AS3MT gene region and reduced AS3MT mRNA expression	Blood / Skin (Human)	Human peripheral blood (Argentinian women)	188 µg/L mean total urinary arsenic (unspecified)	(Engström et al., 2013)
Population response					
Hypermethylation of genes related to diseases associated with inorganic arsenic (e.g., cancer, heart disease, diabetes)	182 hypermethylated genes related to tumor suppression (e.g., forkhead box F1 [FoxF1], matrix metallopeptidase 15 [MMP15])	Peripheral blood lymphocytes (Human)	Females (n= 8) with inorganic arsenical skin lesions in Zimapan, Hidalgo State, Mexico; compared to females (n=8) without lesions	63.47 µg/g total arsenic in urinary creatinine (average) (unspecified)	(Smeester et al., 2011)
Inorganic arsenic induced bladder cancer risk	Promoter methylation silencing of tumor suppressor genes (p16, RASSF1A, PRSS3) and soluble Frizzled receptor proteins (SFRPs) in 30-50% of bladder cancer cases	Bladder tumors (Human)	Participants in population-based case-control of bladder cancer in New Hampshire, U.S.	≤ 0.26 µg/g toenail arsenic (unspecified)	(Marsit et al., 2006c; Marsit et al., 2006b)

Key Events	Observations	Observation Organ System	Test System Observed in	Dose (Exposure duration)[a]	References
Inorganic arsenic-induced skin cancer risk	Dose-related increase in hypermethylation of p53 gene in inorganic arsenic exposed individuals compared to controls & individuals with inorganic arsenic-induced skin cancer patients	Blood (Human)	Human subjects in Kolkata, India (individuals with inorganic arsenic associated skin cancer & nonarsenic cancer)	Controls: <50 µg/L inorganic arsenic in drinking water Exposed: 51-1000 µg/L inorganic arsenic in drinking water (9.5 – 19 yrs)	(Chanda et al., 2006)
Inorganic arsenic induced skin lesions	development of skin lesions associated with low folate	Skin/Blood (Human)	PBL DNA in individuals with skin lesions	2-250 µg/L As(III) (>2 yrs)	(Pilsner et al., 2009)

[a]Abbreviations used for exposure durations: minutes (min), hours (hr), days (d), weeks (wks)

[b]Exposure durations are characterized as "unspecified" when a study does not explicitly state the exposure duration

10.4Preliminary Data on Effects Mediated By the Immune System

Relevant Health Effects: Suppression of humoral immunity (i.e., decreased antibody response), Suppression of innate immunity (decreased macrophage function), Respiratory infection, Gastrointestinal infection, Contact hypersensitivity response

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Molecular Initiating Events					
Molecular initiating events for inorganic arsenic immunotoxicity are unknown. • There is some suggestion that generation of ROS may lead to some immune effects. For example, T-cell apoptosis appears through a ROS-dependent pathway [e.g., (Gupta et al., 2003; Park et al., 2003)] • There is also evidence the effects on macrophages (and therefore many of the effects on the innate immune system which are associated with macrophage function) are unrelated to increased production of ROS. For example arsenic trioxide alters macrophage gene expression through a pathway independent of ROS production, and EGR2 may be one of the molecular targets of inorganic arsenic (Bourdonnay et al., 2009)					
Biochemical Responses					
↓ATP-mediated Ca(2+) signaling	↓wound-induced healing and peak Ca(2+)	Lung (Human)	Immortalized human bronchial epithelial cells (16HBE14o-) in vitro	0, 130, or 330 nM arsenic as sodium arsenite (4-5 wk)	(Sherwood et al., 2013)
	↓wound-induced total Ca(2+) signaling	Lung (Mice)	C57Bl6 male mice ex vivo	50 ppb sodium arsenite drinking water (4 wk)	(Sherwood et al., 2013)
	↓wound-induced healing, Ca(2+), and # cells in Ca(2+) wave	Lung (Human)	Immortalized human bronchial epithelial cells (16HBE14o-) in vitro	0.8 or 3.9 µM sodium arsenite (24 hr)	(Sherwood et al., 2011)
↓ production of interleukin-2 (IL-2), interferon-gamma (IFN-gamma)	↓IL-2, ↓IFNγ, and ↓IL-4 secreted protein from splenocytes in culture, ConA or anti-CD3 stimulated	Spleen (Mice)	C57Bl6 male mice in vitro [young or aged mice (IL-10 also ↓ from old mice)]	0, 0.03, 0.06, 0.13, 0.25, 0.50, 1, 2 µM Sodium arsenite (48 hr)	(Cho et al., 2012)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	↓IL-2, ↓IFNγ, ↓ IL-4 and ↓IL-12 secreted protein from splenocytes in culture, ConA or anti-CD3/CD28 stimulated	Spleen (Mice)	Male C57Bl/6N mice in vivo	0, 0.01, 0.1, 1mg/kg sodium arsenite i.g. (30 days)	(Soto-Peña and Vega, 2008)
	↓IL-2, ↓IFNγ secreted protein and mRNA level from splenocytes in culture anti-CD3/CD28 stimulated	Primary T-cells (Human)	Human T-cells from PBMCs from healthy donors in vitro	0, 0.25, 0.50, 1, 2 µM Sodium arsenite (6 or 24hr)	(Morzadec et al., 2012)
↓ production of interleukin-2 (IL-2), interferon-gamma (IFN-gamma) *(continued)*	↓IL-2 secreted protein levels from PHA-stimulated mononuclear cells; no difference in IFNγ, IL-4, IL-10	Primary monocytes differentiated in 6 days into macrophages (Human)	Human monocytes from PBMCs from children (6-10) living in central Mexico chronically exposed to As in drinking water	Low exposure group: Girls: 11.8 µg/l Boys: 15.6 µg/l urinary As (mean) High exposure group: Girls: 88.2 µg/l Boys: 84.4 µg/l) urinary As (mean) (unspecified)[b]	(Soto-Peña et al., 2006)
	↓IL-2 secreted protein levels from PHA-stimulated mononuclear cells	Primary mononuclear cells (Human)	Human PBMCs from healthy donors in vitro	0, 0.01, 0.1, 1 µM Sodium arsenite (24 – 48 hr)	(Galicia et al., 2003)
	↓IL-2 secreted protein level PHA-stimulated mononuclear cells	Primary mononuclear cells (Human)	Human PBMCs from healthy donors in vitro	0, 0.01, 0.1, 1µM Sodium arsenite (24-48 hr)	(Vega et al., 1999)
	↓IL-2 at protein and mRNA level ↓IL-2 splenocytes in culture, PHA-stimulated	Spleen (Mice)	C57Bl6 female mice in vitro	0, 1, 10 µM sodium arsenite (12, 24, 48 hr)	(Conde et al., 2007)
	↓IL-2, ↓IFNγ, ↓IL-4, ↓TNFα, ↓IL-10, ↓IL-5 secreted protein in culture, ConA stimulated	Primary T-cells (Human)	Human T-cells from PBMCs from exposed and unexposed donors	20 individuals with skin lesions compared to 18 unexposed	(Biswas et al., 2008)
	↓IL-2 secreted	Spleen	Chicken in	1 and 10 µM	(Das et

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	protein from splenocytes in culture, and both↓IL-2 ↓IFNγ at mRNA level, ConA stimulated	(Chicken)	vitro	sodium arsenite (24, 48, 72 hr)	al., 2011)
↓proliferation of lymphocytes	↓ConA-stimulated T-cell proliferation in culture [^{3}H] TdR incorporation	Primary T-cells (Human)	Human T-cells from PBMCs from exposed and unexposed donors	20 individuals with skin lesions compared to 18 unexposed	(Biswas et al., 2008)
	↓ConA-stimulated T-cell proliferation in culture [^{3}H] TdR incorporation	Spleen (Rats)	Male Wistar rats in vivo	25 ppm sodium arsenite in drinking water (42 days)	(Sankar et al., 2013)
	Slower proliferation response to PHA- T-cell in culture [^{3}H] TdR incorporation	Primary T-cells (Human)	Human T-cells from PBMCs from exposed (33 individuals from an area in Mexico) and unexposed (30) donors	Exposed: 412 µg/l As in water (758±364 µg/l total As in urine) Unexposed: 37µg/l in water (37±37µg/l total As in urine)	(Gonsebatt et al., 1994)
↓proliferation of lymphocytes *(continued)*	↓PHA-stimulated T-cell proliferation in culture [^{3}H] TdR incorporation	Primary mononuclear cells (Human)	Human PBMCs from healthy donors in vitro	0, 0.01, 0.1, 1µM Sodium arsenite (24-48 hr)	(Vega et al., 1999)
	↓PHA-stimulated T-cell proliferation in culture [^{3}H] TdR incorporation	Primary monocytes differentiated in 6 days into macrophages (Human)	Human monocytes from PBMCs from children (6-10) living in central Mexico chronically exposed to As in drinking water	Low exposure group: Girls: 11.8 µg/l Boys: 15.6 µg/l urinary As (mean) High exposure group: Girls: 88.2 µg/l Boys: 84.4 µg/l) urinary As (mean)	(Soto-Peña et al., 2006)
Cell signaling change	NF-κB (↑phosphorylated p65)	Lung (Mice)	Nrf2-WT and Nrf2-KO mice in vivo	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert dust] (30 min/day/14d)	(Zheng et al., 2012)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	NF-κB (↓ DNA binding of p65 NF-κB)	Primary monocytes and pro-monocyte cell line (Human)	Human monocytes from PBMCs from healthy donors and pro-monocytic U937 cell line in vitro	0.25-1 µM arsenic trioxide (1, 2, 3, 4, 6 days)	(Lemarie et al., 2006)
	↓enzymatic activity of lysosomal protease cathepsin L	Primary lymphocytes (Human)	Human PBMCs from blood of healthy volunteers In vitro	0, 1, 2, 3, 4, 5µM arsenic trioxide (48hr)	(Gupta et al., 2003)
	↓transcription factor ERG2	Primary monocytes differentiated into macrophages (Human)	Human monocytes from PBMCs from healthy donors in vitro	1µM arsenic trioxide (48, 72 hr)	(Bourdonnay et al., 2009)
	↑basal phosphorylation of Lck and Fyn kinases and ↑ phosphorylation of Lck and Fyn after stimulation by antibodies to CD3/CD28 in splenocytes	Spleen (Mice)	Male C57Bl/6N mice in vivo	0, 0.01, 0.1, 1 mg/kg sodium arsenite intra-gastric (30 days)	(Soto-Peña and Vega, 2008)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Cellular Phenotypic Changes					
↓monocyte/ macrophage activity or number	↓monocyte recruitment to peritoneal cavity following thioglycollate stimulation	Macrophages (Mice)	Female balb/c mice in vivo	50 mg/L sodium metaarsenite in drinking water (4 wks)	(Patterson et al., 2004)
	↓differentiation monocytes to macrophages by expression of transferrin receptor CD71	Primary monocytes and pro-monocyte cell line (Human)	Human monocytes from PBMCs from healthy donors and pro-monocytic U937 cell line in vitro	0.25-1 µM arsenic trioxide (1, 2, 3, 4, 6 days)	(Lemarie et al., 2006)
	↑apoptosis of splenic macrophages indicated by DNA fragmentation	Spleen (Mice)	Male Swiss albino mice in vivo	0.5 sodium arsenite mg/kg bw/day (15 days)	(Sengupta and Bishayi, 2002)
	↑apoptosis of monocytes, macrophages by Annexin V-Alexa568 (A5) and SG co-staining	Primary monocytes and pro-monocyte cell line (Human)	Human monocytes from PBMCs from healthy donors and pro-monocytic U937 cell line in vitro	0.25-1µM arsenic trioxide (1, 2, 3, 4, 6 days)	(Lemarie et al., 2006)
	↑ basal apoptosis of monocytes, macrophages by PI staining and analysis for hypodiploid cells	Primary monocytes (Human)	Human monocytes from children chronically exposed to As and nearby unexposed children	Urinary As range from 94 to 240µg/g-creatinine exposed children living in town near gold mine, 17-34µg/g-creatinine in nearby unexposed children	(de la Fuente et al., 2002)
	↑ apoptosis of monocytes, macrophages by DNA content assay, Annexin V binding, DNA fragmentation, TUNEL	Primary monocytes (Human)	Human monocytes from PBMCs from healthy donors in vitro	0, 1, 5, 15,30, 50, 75, 100µM sodium arsenite (12, 36, 48, 72 hr)	(de la Fuente et al., 2002)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
↓monocyte/ macrophage activity or number *(continued)*	↑macrophage cell rounding, ↓adhesion, ↓phagocytosis of *S. typhimurium* in 3h, ↓NO^- and O_2^- following LPS stimulation overnight	Primary monocytes differentiated in 6 days into macrophages (Human)	Human monocytes from PBMCs from individuals) in West Bengal India with skin lesions (n= 70) chronically exposed to As in drinking water (Murshidabad) and unexposed (n=64) (West Midnapore	Exposed individuals: 50 to 1,200 µg/L aresenic in drinking water levels Unexposed individuals: levels 3 to 10 µg/L inorganic arsenic in drinking water	(Banerjee et al., 2009)
	Splenic macrophages ↓NO^- and O_2^- after LPS stimulation, ↓macrophage adhesion, ↓chemotaxis, ↓phagocytosis of SRBCs	Spleen (Mice)	Male Swiss albino mice in vivo	0.5 sodium arsenite mg/kg bw/day (15 days)	(Sengupta and Bishayi, 2002)
	↓macrophage phagocytosis of *A. hydrophila*	Macrophages (Catfish)	Catfish in vivo	42.42 µM arsenic trioxide (21 days)	(Ghosh et al., 2006)
	↑macrophage abnormal morphology, ↓adhesion, ↓chemotaxis	Spleen (Mice)	Male Swiss albino mice in vivo	0.5 mg/kg bw (intraperitoneal injection) sodium arsenite (15 days)	(Bishayi and Sengupta, 2003)
	↓ monocyte /macrophage ROS after PMA, ↓ NO^- after RD-F or LPS stimulation	Primary monocytes (Chicken)	Chicken monocytes from PBMCs in vivo	3.7 ppm sodium arsenite in drinking water (10, 20, 30, 40, 60 days)	(Aggarwal et al., 2008)
	↓ monocyte /macrophage ROS after PMA, ↓ NO^- after LPS stimulation	Spleen and peritoneal macrophages (Mice)	Female c57BL7J/Han mice	0, 0.5, 5, 50 sodium hydrogen arsenate (12 wks)	(Arkusz et al., 2005)
	↑apoptosis of monocytes, macrophages by	Primary monocytes and pro-	Human monocytes pro-	0, 0.5, 1, 2.5, 5µM tetraarsenic oxide and diarsenic oxide	(Park et al., 2003)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	Annexin V—FITC and PI staining	monocyte cell line (Human)	monocytic U937 cell line in vitro	(0, 2, 4, 6, 8, 10, 12 hr)	
↑neutrophil apoptosis	↑neutrophil apoptosis determined by CD16 shedding independent of MAPKs	Human (Lung)	Human neutrophils from venous blood of healthy volunteers In vitro	5 µM arsenic trioxide (.25 – 180 minutes)	(Binet and Girard, 2008)
↑T-lymphocyte apoptosis	↑T-cell apoptosis determined by TUNEL assay	Primary lymphocytes (Human)	Human PBMCs from blood of healthy volunteers In vitro	0, 1, 2, 3, 4, 5 µM arsenic trioxide (48 hr)	(Gupta et al., 2003)
↑ B-lymphocyte apoptosis	↑B-cell apoptosis determined by Annexin V assay	Lymphocytes (Mice)	Mouse B cell lymphoma line TA3 In vitro	0, 0.8, 4, 20, 100, 500 µM sodium arsenite (18 hr)	(Harrison and McCoy, 2001)
↓Langerhans cell migration	↓activated Langerhans cells in cervical lymph nodes of DNFB-sensitized mice by fluorescence-activated sorting	Immune, Skin (Mice)	Female balb/c mice in vivo	50 mg/l sodium metaarsenite in drinking water (4 wks)	(Patterson et al., 2004)
Tissue/ Organ Responses					
↓Thymus size	↓Thymus size assessed sonographically	Thymus (Human)	Children in Matlab region of Bangladesh cohort	Maternal arsenic metabolites in urine at weeks 8 and 30 of gestation	(Moore et al., 2009; Raqib et al., 2009)
	↓absolute, not relative thymus weight	Thymus (Chicken)	Chickens in vivo	3.7 ppm sodium arsenite in drinking water (10, 20, 30, 40, 60 days)	(Aggarwal et al., 2008)
Individual Responses					
↓delayed-type hypersensitivity (DTH) response	↓DTH to KLH by footpad thickness	Immune function (Rats)	Male Wistar rats in vivo	25 ppm sodium arsenite in drinking water (42 days)	(Sankar et al., 2013)
	↓DTH to 2,4-dinitro-1-chlorobenzene (DNCB) or PHA-P by	Immune function (Chicken)	Chickens in vivo	3.7 ppm sodium arsenite in drinking water (10, 20, 30, 40, 60	(Aggarwal et al., 2008)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	skin thickness			days)	
	↓phytohemagglutin in hypersensitivity response by skin thickness	Immune function (Rats)	Male cotton rats	0, 5, 10 ppm sodium arsenite (6 wks)	(Savabieasfahani et al., 1998)
↓antibody response	↓decreased antibody response by ELISA to vaccination with disease virus (F-strain; RD-F)	Immune function (Chicken)	Chickens in vivo	3.7 ppm sodium arsenite in drinking water (10, 20, 30, 40, 60 days)	(Aggarwal et al., 2008)
↓antibody response *(continued)*	↓antibody response by agglutination to bacterial (*A. hydrophila*) challenge; ↓antigen-specific plaque-forming cells to SRBC	Immune function (Catfish)	Catfish in vivo	42.42 µM arsenic trioxide (150 days)	(Ghosh et al., 2007a)
	↓antibody response to SRBC by PFC	Immune function (Mice)	Male c57bl/6N mice in vivo	50 µg/m^3 and 1 mg/m^3 nose only inhalation arsenic trioxide (14 days)	(Burchiel et al., 2009)
	↓antibody response for IgG at day 14 to KLH by ELISA; not significant in IgM at day 5	Immune function (Mice)	Male Wistar rats in vivo	0, 0.4, 4, 40 ppm sodium arsenite in drinking water (18 wks)	(Nain and Smits, 2012)
	↓antibody response to SRBC by PFC	Immune function (Mice)	Male white Swiss cross mice in vivo	0, 0.5, 2, 10 ppm sodium arsenite in drinking water (3 wks)	(Blakley et al., 1980)
↓host resistance (to infection)	↓ ability to decrease bacteria load (*C. batrachus*), ↑tissue damage, slower recovery, ↑mortality	Immune function (Catfish)	Catfish in vivo	42.42 µM arsenic trioxide (150 days)	(Ghosh et al., 2007a)
	↓ blood and splenic clearance bacterial (*S. aureus)* challenge	Immune function (Mice)	Male Swiss albino mice in vivo	Sodium arsenite (p.5 mg/kg bw (ip) (15 days)	(Bishayi and Sengupta, 2003)
	↓ability to clear viral (snakehead	Immune function	Zebrafish in	2 or 10ppb sodium arsenite in water	(Nayak et

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	rhabovirus) or bacterial (*E. tarda*)load	(Zebrafish)	vivo	(4 days starting at 1 cell stage)	al., 2007)
	Respiratory infection ↑ influenza virus titer and ↑virus-related morbidity	Immune function (Mice)	Male C57bl/6j mice in vivo	100ppb sodium arsenite in drinking water (5 wks)	(Kozul et al., 2009)
↓contact sensitization response	↓Lymph node proliferation; ↓ear swelling to DNFB	Immune, Skin (Mice)	Female balb/c mice in vivo	50 mg/l sodium metaarsenite in drinking water (4 wks)	(Patterson et al., 2004)
Susceptible individual response					
NALP2 gene polymorphism (C/A +A/A) of NLP2 A1052E SNPs	NALP2 gene polymorphism modifies inorganic arsenic-associated respiratory disease	Immune / Respiratory (Human)	Individuals from West Bengal all with inorganic arsenic exposure; case-control study divided by presence of inorganic arsenic-related skin lesions	Exposure assessed by inorganic arsenic content of drinking water and urine samples	(Bhattacharjee et al., 2013)
TNFα and IL10 gene polymorphism (-308G/A and -3575T/A)	GA/AA TNFα genotype had higher risk of developing inorganic arsenic-induced conjunctivitis and respiratory effects; TNFα (pro-inflammatory cytokine) and IL10 (anti-inflammatory cytokine) gene polymorphisms modify serum TNFα and IL10 levels	Immune / Respiratory / eye (Human)	Individuals from West Bengal all with inorganic arsenic exposure; case-control study divided by presence of inorganic arsenic-related skin lesions	Arsenic exposure assessed in urine	(Banerjee et al., 2011)
Population Response					
Respiratory infection	↑ relative risk of lower respiratory tract infection, ↑relative risk of	Immune/ Respiratory (Human)	Children in Matlab region of Bangladesh MINIM	262 – 977 µg/L maternal arsenic metabolites in urine (average)	(Rahman et al., 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	sever lower respiratory tract infection		cohort	compared to <39 µg/L maternal arsenic metabolites in urine	
	↑acute respiratory infection	Immune/ Respiratory (Human)	Children in Matlab region of Bangladesh cohort	152.4, 145.8 µg/L maternal arsenic metabolites in urine (mean) at weeks 8 and 30 gestation	(Raqib et al., 2009)
	↑ relative risk of lower and upper respiratory tract infection requiring physician visit or prescription medication, and ↑respiratory symptoms,	Immune/ Respiratory (Human)	Children New Hampshire Birth Cohort	6 µg/L maternal urinary As levels (mean) at 24-28 weeks gestation	(Farzan et al., 2013)
Disease/cold fever	↑ days of fever	Immune (Human)	Pregnant mothers in Matlab region of Bangladesh cohort	152.4, 145.8 µg/L maternal arsenic metabolites in urine (mean) at weeks 8 and 30 gestation	(Raqib et al., 2009)
	↑colds treated with prescription	Immune (Human)	Children New Hampshire Birth Cohort	6 µg/L maternal urinary As levels(mean) at 24-28 weeks gestation	(Farzan et al., 2013)
Infection-related GI disease	↑ relative risk of diarrhea	Immune/ gastro-intestinal (Human)	Children in Matlab region of Bangladesh MINIM cohort	262 – 977 µg/L maternal arsenic metabolites in urine (average) compared to <39 µg/L maternal arsenic metabolites in urine	(Rahman et al., 2011)
	↑ days of diarrhea	Immune/ gastro-intestinal (Human)	Pregnant mothers in Matlab region of Bangladesh cohort	152.4, 145.8 µg/L maternal arsenic metabolites in urine (mean) at weeks 8 and 30 gestation	(Raqib et al., 2009)
	↑diarrhea symptoms lasting two or more days or requiring doctors visit were associated but not significant [RR=1.9(0.9,3.9) and	Immune/ Respiratory (Human)	Children New Hampshire Birth Cohort	6 µg/L maternal urinary As levels (mean) at 24-28 weeks gestation	(Farzan et al., 2013)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	RR=3.5 (0.8,15.4)]				

[a]Abbreviations used for exposure durations: minutes (min), hours (hr), days (d), weeks (wks)

[b]Exposure durations are characterized as "unspecified" when a study does not explicitly state the exposure duration

10.5Preliminary Data on Effects Mediated By Oxidative Stress

Relevant Health Effects: Cardiovascular Disease, Diabetes, Liver Disease, Lung Cancer, Bladder Cancer, Neurotoxicity, Non-Malignant Respiratory Disease, Pregnancy Outcomes, Renal Disease, Skin Cancer, and Skin Lesions

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
Molecular Initiating Events					
Reaction with O_2 (intermediate arsine species; e.g., dimethylarsine)	↑free radicals (e.g., Dimethylarsenic peroxyl radical [$(CH_3)_2AsOO$], superoxide anion)	Multiple (See Review Article)	Multiple (See Review Article)	Multiple (See Review Article)	Reviewed in (Flora, 2011)
Reaction with ferritin (Methylated-As)	Redox-active Fe release	Multiple (See Review Article)	Multiple (See Review Article)	Multiple (See Review Article)	Reviewed in (Flora, 2011)
Oxidation of As(III) to As(V)	H_2O_2 formation followed by Fenton reaction (hydroxyl radical formation)	Multiple (See Review Article)	Multiple (See Review Article)	Multiple (See Review Article)	Reviewed in (Flora, 2011; Jomova and Valko, 2011)
Reactions with NADPH oxidase	↓ROS with NADPH inhibitor	Liver (Human)	Human immortalized liver cell line HL-7702	Diphenylene-iodonium chloride (DPI) (30 min pretreatment) + 5 µM arsenite (2 hr)	(Li et al., 2014); Reviewed in (Flora, 2011)
Reactions with mitochondrial respiratory chain	↓ROS with mitochondrial respiratory chain inhibitor	Liver (Human)	Human immortalized liver cell line HL-7702	Rotenone (30 min pretreatment) + 5 µM arsenite (2 hr)	(Li et al., 2014); Reviewed in (Flora, 2011)
Biochemical Responses					
Generation of reactive oxygen species	↓dichlorofluorescein diacetate (peroxides)	Skin (Human)	HaCaT transformed keratinocytes	0.5 µM trivalent arsenic (As[III]) (24 hr)	(Snow et al., 2005)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
		Lung (Human)	WI38 human diploid lung fibroblast	0.5 µM trivalent arsenic (As[III]) (24 hr)	
	↑H_2O_2 ↑Superoxide	Lung (Rat)	Lung Epithelial Cells (LECs)	≤ 1 µM sodium arsenite (30 min)	(Li et al., 2011)
	↑Superoxide	Liver (Mouse)	Liver Sinusoidal Endothelial Cells (SECs)	2.5 – 5 µM arsenite (30 min)	(Straub et al., 2008)
Generation of reactive oxygen species (*continued*)	↑ 2',7'-dichlorofluorescein-diacetate (DCFH-DA)	Liver (Human)	Human immortalized liver cell line HL-7702	5 µM arsenite (2 hr)	(Li et al., 2014)
	↑H_2O_2 *co-treatment with anti-oxidants prevents ↑	Liver (Rat)	Wistar Rats (Male, albino) (liver microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
		Kidney (Rat)	Wistar Rats (Male, albino) (kidney microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
	Dose dependent ↑CM-H_2DCFDA fluorescence (general ROS indicator) * co-treatment with anti-oxidants mitigates ↑ *latent ↑ with MMA(III) compared with As(III) (no ↑ at 10 min)	Urothelium (Human)	UROtsa cells	1-100 µM $NaAsO_2$ (10 min) 50 500 nM MMA(III) (30 min)	(Eblin et al., 2006)
	↑CM-H_2DCFDA * co-treatment with anti-oxidants mitigates ↑	Urothelium (Human)	UROtsa cells	10 µM $NaAsO_2$ (10 min) 500 nM MMA(III) (10 min)	(Eblin et al., 2008)
	Time-dependent ↑CM-H_2DCFDA fluorescence *significant ↑ only at 12 weeks	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (4 - 12 weeks)	(Wnek et al., 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
Mitochondrial Activity Changes	↑colocalization of ROS & mitochondria staining	Liver (Human)	Human immortalized liver cell line HL-7702	5 µM arsenite (2 hr)	(Li et al., 2014)
Alteration in glutathione and other non-enzymatic antioxidant levels	↓GSH	Brain (Mouse)	Swiss Mice (Male albino)	0.5 or 1 As_2O_3 mg/kg (45 days)	(Rao and Avani, 2004)
		Brain (Rat)	Sprague Dawley Rats (Male)	0.05, 0.10, 0.30, 3.0 ppm Na_3AsO_4 (40 days)	(Chaudhuri et al., 1999)
		Lung (Rat)	Lung Epithelial Cells (LECs)	2 µM sodium arsenite (≤ 30 min)	(Li et al., 2011)
Alteration in glutathione and other non-enzymatic antioxidant levels (*continued*)	↓GSH ↓Ascorbic acid ↓α-tocopherol *co-treatment with anti-oxidants prevents ↓	Liver (Rat)	Wistar Rats (Male, albino) (liver microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
		Kidney (Rat)	Wistar Rats (Male, albino) (kidney microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
	↑GSH	Pancreas (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/ 90 days)	(Izquierdo-Vega et al., 2006)
		Pancreas (Rat)	INS-1(832/13) cells (Rat β-cells)	0.25 -0.5 µM arsenite (96 hr)	(Fu et al., 2010)
		Lung (Rat)	Lung Epithelial Cells (LECs)	2 µM sodium arsenite (2-8 hr)	(Li et al., 2011)
Depletion of micronutrients	↓ascorbate ↓ Fe(II)	Liver (Human)	Human immortalized liver cell line HL-7702	5 µM arsenite (12 hr)	(Li et al., 2014)
Enzyme Activity Changes	↓SOD dismutase ↓catalase	Brain (Mouse)	Swiss Mice (Male albino)	0.5 or 1 mg/kg As_2O_3 (45 days)	(Rao and Avani, 2004)
	↓SOD dismutase ↓catalase ↓glutathione reductase	Brain (Rat)	Sprague Dawley Rats (Male)	0.05, 0.10, 0.30, 3.0 ppm Na_3AsO_4 (40 days)	(Chaudhuri et al., 1999)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
	↑DNA ligase	Lung (Human)	WI38 human diploid lung fibroblast	0.5 – 1 µM As(III) (24 to 120 hr)	Reviewed in (Snow et al., 2005)
	↓ DNA ligase			5 or 10 µM As(III) (24 to 120 hr)	
	Rac1-GTPase activation NADPH Oxidase activation (Nox2-based)	Liver (Mouse)	C57BL/6 Tac Mice (In-vivo and ex-vivo liver sinusoidal endothelial cells [SECs])	In vivo: 250 ppb sodium arsenite (5 wk) Ex vivo: 2.5 µM sodium arsenite (8 hr)	(Straub et al., 2008)
	↑ NADPH Oxidase (inferred) ↑Propyl hydroxylase (PHDs) (inactivates HIF-1α)	Liver (Human)	Human immortalized liver cell line HL-7702	5 µM arsenite (12 hr)	(Li et al., 2014)
Enzyme Activity Changes (*continued*)	↑haem oxygenase ↓Cytochrome P450 ↓Cytochrome b5 ↓NADPH-cyt P450 reductase *↑/↓ mitigated by antioxidants	Liver (Rat)	Wistar Rats (Male, albino) (liver microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
		Kidney (Rat)	Wistar Rats (Male, albino) (kidney microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
	↓thioredoxin reductase (TrxR)	Pancreas (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/ 90 days)	(Izquierdo-Vega et al., 2006)
	↓poly(ADP-ribose) polymerase-1 (PARP-1) *↑ activity if MMA(III) exposure is discontinued for 2 weeks prior to measurement in cells previously exposed for 4 or 8 weeks	Urothelium (Human)	UROtsa cells	50 nM MMA(II) (4-12 weeks)	(Wnek et al., 2011)
Protein expression and/or level changes	Western Blot: ↑Base excision repair proteins (DNA polymerase β, DNA ligase I)	Skin (Human)	Human Keratinocyte Cells (HaCaT)	0.1 - 1 µM As(III) (24 hr)	Reviewed in (Snow et al., 2005)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
	↓ Base excision repair proteins			5 - 10 µM As(III) (24 hr)	
	Western Blot: ↑Base excision repair proteins (DNA polymerase β, DNA ligase I) ↓ Base excision repair proteins	Lung (Human)	WI38 human diploid lung fibroblast	0.1 - 1 µM As(III) (24 hr) 5 - 10 µM As(III) (24 hr)	Reviewed in (Snow et al., 2005)
	mRNA & Western Blot: ↑NRF1 ↑NRF2	Skin (Human)	Immortalized human keratinocyte cells (HaCaT)	>5 µM inorganic arsenite (As[III]) (6 hr)	(Zhao et al., 2012)
Protein expression and/or level changes (*continued)*	Western Blot: ↑Nrf2	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
	Western Blot: ↑Cu/Zn SOD, thioredoxin *mitigated by antioxidants	Lung (Rat)	Lung Epithelial Cells (LECs)	2 µM sodium arsenite (16 weeks)	(Li et al., 2011)
	Immunofluorescence: ↑PECAM-1	Liver (Mouse)	C57BL/6 Tac Mice (In-vivo and ex-vivo liver sinusoidal endothelial cells [SECs])	In vivo: 250 ppb sodium arsenite (5 wk) Ex vivo: 1-5 µM sodium arsenite (8 hr)	(Straub et al., 2008)
	Western Blot: ↑HIF-1α	Liver (Human)	Human immortalized liver cell line HL-7702	5 µM arsenite (12 hr)	(Li et al., 2014)
	Western Blot: ↑VEGF	Liver (Human)	Human immortalized liver cell line HL-7702	1—5 µM arsenite (12 hr)	(Li et al., 2014)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
	Western Blot: ↑Nrf nuclear fraction *↑ARE luciferase activity; ↑expression of downstream targets mRNA (e.g., Hmox1, NAD(P)H, catalase)	Pancreas (Rat)	INS-1(832/13) cells (Rat β-cells)	0.25 -0.5 µM arsenite (96 hr)	(Fu et al., 2010)
	Western Blot: ↑Hsp70 (stress protein)	Urothelium (Human)	UROtsa cells	1 µM $NaAsO_2$ (30 min) 10 µM $NaAsO_2$ (30-240 min)	(Eblin et al., 2006)
				50 nM – 5 µM MMA(III) (30 – 240 min)	
	Western Blot: ↑metallothionein (stress protein)			1 µM $NaAsO_2$ (240 min) 10 µM $NaAsO_2$ (30-240 min)	
				50 nM – 5 µM MMA(III) (30 – 240 min)	
Protein expression and/or level changes (*continued)*	mRNA & Western Blot: ↑PARP-1 *no effect on expression if MMA(III) exposure is discontinued for 2 weeks prior to measurement in cells previously exposed for 4 or 8 weeks	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (4-12 weeks)	(Wnek et al., 2011)
	Western blot: ↑ Cox-2 *levels normalize by 24 hr **co-treatment with SOD or melatonin block induction; no effect of catalase	Urothelium (Human)	UROtsa cells	1 µM sodium arsenite (4 hr); or 50 nM MMA(III) (4 hr)	(Eblin et al., 2008)
	mRNA: ↑ Cox-2 *levels normalize by 24 hr **co-treatment with catalase, SOD or melatonin block induction	Urothelium (Human)	UROtsa cells	1 µM sodium arsenite (4 hr); or 50 nM MMA(III) (4 hr)	(Eblin et al., 2008)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
	Western blot: ↓Mn SOD *no change in Mn SOD with As(III) treatment; very little change in catalase with either As(III) or MMA(III) treatments	Urothelium (Human)	UROtsa cells	50 nM MMA(III) (1 to 24 hr)	(Eblin et al., 2008)
	Western blot: ↑Cu/Zn SOD *↓after 24 hr MMA(III) exposure	Urothelium (Human)	UROtsa cells	1 µM sodium arsenite (0.5 -24 hr) 50 nM MMA(III) (0.5 -4 hr)	(Eblin et al., 2008)
Cell membrane disruption	↑Lipid peroxidation	Brain (Mouse)	Swiss Mice (male albino)	0.5 or 1 mg/kg As_2O_3 (45 days)	(Rao and Avani, 2004)
		Brain (Rat)	Sprague Dawley Rats (Male)	0.05, 0.10, 0.30, 3.0 ppm Na_3AsO_4 (40 days)	(Chaudhuri et al., 1999)
		Liver (Mouse)	BALB/c Mice (Male)	3.2 mg/L As(III)/As(V) (6 months)	(Santra et al., 2000)
		Liver (Rat)	Wistar Rats (Male, albino) (liver microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
Cell membrane disruption (*continued)*	↑Lipid peroxidation (continued)	Kidney (Rat)	Wistar Rats (Male, albino) (Kidney microsomes)	100 ppm sodium arsenite (30 days)	(Ramanathan et al., 2003)
		Pancreas (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/ 90 days)	(Izquierdo-Vega et al., 2006)
DNA, chromosomal damage	Oxidative DNA damage (↑anti-8-Oxo-dG staining)	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
	Oxidative DNA damage (↑ 8-OHdG staining)	Blood (Human)	Human Population	10.88 to 19.05 µg/gCr urinary arsenic (40-70 yrs)	(Pei et al., 2013)
	Oxidative DNA damage (↑anti-8-Oxo-dG levels measured by HPLC/ECD)	Urothelium (Human)	UROtsa cells	1 – 10 µM $NaAsO_2$ (30 min)	(Eblin et al., 2006)
				50 nM MMA(III) (30)	
				50 nM – 5 µM MMA(III) (60 min)	
	↓anti-8-Oxo-dG levels measured by HPLC/ECD			1 – 10 µM $NaAsO_2$ (60 min)	
	↑DNA single-strand breaks (comet assay and flow cytometry)	Urothelium (Human)	UROtsa cells	50 nM MMA(II) (4-12 weeks)	(Wnek et al., 2011)
Gene expression changes	↑NRF2 & ARE dependent genes (HMOX-1, NQo1, GCLC, GCLM, SRX)	Skin (Human)	Immortalized human keratinocyte cells (HaCaT)	1.25-40 µM inorganic arsenite (As[III]) (6 hr)	(Zhao et al., 2012)
	↑Nrf2 targets (NQ01, γGCS, HO-1)	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
Gene expression changes (*continued)*	Altered gene expression related to: oxidative stress (↑HMOX1); protein folding (↓FKB5) Thioredoxin reductase (↑TXNRDI) Metallothinonine regulation (↑MT1E) DNA damage sensing (↓DDB2) Thioredoxin (↑TXN) Cell adhesion/growth (↑LGALS8) Immune response (↓THBD)	Urothelium (Human)	Human uroepithelial cells from kidney donor ureter segments	6 µM As(III) +MMA^{V}+DMA^{V} (24 hr); or 6 µM As(III) +MMA^{3+} +DMA^{3+} (24 hr)	(Yager et al., 2013; Clewell et al., 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
	Alterations in genes related to: inflammatory signaling, epithelial-to-mesenchymal transition, cell cycle control, and apoptosis/survival signaling	Urothelium (Human)	Human uroepithelial cells from kidney donor ureter segments	0.06 µM inorganic arsenic and trivalent or pentavalent metabolites (24 hr)	(Clewell et al., 2011)
	↑adaptive gene response (delay apoptosis, preinflammatory)	Various	Various	≤ 0.01 µM various arsenic species (various exposure durations)	(Gentry et al., 2010) Review
	Altered gene expression related to: Oxidative stress, proteotoxicity, inflammation, and proliferative signaling, DNA repair, cell cycle, G2/M checkpoint control, and induction of apoptosis	Various	Various	0.1 – 10 µM various arsenic species (various exposure durations)	(Gentry et al., 2010) Review
	Altered apoptotic gene expression	Various	Various	10 – 100 µM various arsenic species (various exposure durations)	(Gentry et al., 2010) Review
	760 Alternations in gene expression, generally related to: Oxidative stress (e.g., NQO1) Lipid metabolism (e.g., ALDH2) Inflammatory response (e.g., IL8, MAPK1)	Urothelium (Human)	UROtsa cells	1 µM MMA(III) (24 hr)	(Bailey et al., 2012)
Gene expression changes (*continued)*	176 alternations in gene expression, generally related to: Oxidative stress (e.g., TNF) Lipid metabolism (e.g., AKT3) Inflammatory response (e.g., IL8, IL6)	Urothelium (Human)	UROtsa cells	1 µM DMA(III) (24 hr)	(Bailey et al., 2012)
	Genes in ERK 1/2 MAPK- & NF-KB signaling pathways	Urothelium (Human)	UROtsa cells	1 µM MMA(III) or DMA(III) (24 hr)	(Bailey et al., 2012)
Cell signaling changes	Transcription Factors (e.g., Nrf2, HIF-1α, NF-κB)				Reviewed in (Flora, 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
(Numerous; examples provided here—see review article for details)	NF-κB (↑p-p65)	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
	Mitogen-activated protein kinases (MAPKs)				Reviewed in (Flora, 2011)
	Erk (Ras, Raf, MEK, ERK activation)	Lung (Rat)	Lung Epithelial Cells (LECs)	100 µM B[α]P (24hr) 2 µM sodium arsenite (16 wks)	(Li et al., 2011)
	Tyrosine phosphorylation				Reviewed in (Flora, 2011)
	↑p- Epidermal Growth Factor Receptor	Lung (Human)	Transformed human bronchial cells (BEAS)	500 µM sodium arsenite (20 min)	(Wu et al., 1999)
Cellular Responses					
Cytotoxicity/ viability, proliferation, apoptosis	↑cytotoxicity ↑apoptosis	Skin (Human)	Immortalized human keratinocyte cells (HaCaT)	>10 µM As(III) (24 hr)	(Zhao et al., 2012)
	↓cell viability *↑ mitigated by natural Nrf2-inducer	Lung (Human)	Human bronchial epithelium cells (16HBE14o)	≤ 1 µM As(III) (48 hr)	(Tao et al., 2013)
	↑ TUNEL labeling	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
Cytotoxicity/ viability, proliferation,	↑proliferation	Lung (Rat)	Lung Epithelial Cells (LECs)	2 µM sodium arsenite (24 hr)	(Li et al., 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
apoptosis (*continued)*	↑cell viability ↓cell viability *reduced Nrf2 expression sensitizes cells to viability change; activation of Nrf2 mitigates effects	Bladder (Human)	Human bladder urothelium cell line (UROtsa)	5 -10 µM As(III) (24 hr) 20-80 µM As(III) (24 hr)	(Wang et al., 2007b)
	↓ cell viability *co-treatment with antioxidants other than catalase prevents ↓	Bladder (Human)	Human bladder urothelium cell line (UROtsa)	1 µM sodium arsenite, (24 hr)	(Eblin et al., 2008)
	No ↓ cell viability			50 nM MMA(III) (24 hr)	
Epithelial-mesenchymal transition	Colony formation, ↓epithelial protein markers ↑mesenchymal protein markers *mitigated by antioxidant treatment	Lung (Rat)	Lung Epithelial Cells (LECs)	100 µM B[α]P (24hr) 2 µM sodium arsenite (16 wks)	(Li et al., 2011)
Cell matrix changes	↓porosity	Liver (Mouse)	C57BL/6 Tac Mice (In-vivo and ex-vivo liver sinusoidal endothelial cells [SECs])	In vivo: 250 ppb sodium arsenite (5 wk) Ex vivo: 1-5 µM sodium arsenite (8 hr)	(Straub et al., 2008)
Functional Changes	↓insulin production ↓glucagon production	Pancreas (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/ 90 days)	(Izquierdo-Vega et al., 2006)
	↓insulin secretion in response to glucose ↑insulin secretion in response to potasium chloride	Pancreas (Rat)	INS-1(832/13) cells (Rat β-cells)	0.25 -0.5 µM arsenite (96 hr)	(Fu et al., 2010)
Malignant transformation	↑multinucleated cells, morphological changes (confocal microscopy) tumor formation in in vivo xenografts	Urothelium (Human)	UROtsa cells	0.05 µM MMA(III) (24 -52 weeks)	(Bredfeldt et al., 2006)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
Tissue/ Organ Responses					
Tissue remodeling	↑ Alveolar septa thickening, collagen deposition, fibroblast proliferation, pneumocyte hyperplasia;	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
Inflammatory response	↑ inflammatory cells in BAL fluid ↑TNF-α, IL-6 in BAL fluid ↑Th2 cytokines (IL-3, IL-4) ↑chemokines (TGF-β, MCP-1) *↑ mitigated by natural Nrf2-inducer	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
	↑ TNF-α, IL-1β, IFNγ	Placenta (Human)	Human Population	>60 µg/L urinary arsenic at gestational week 30	(Ahmed et al., 2011)
Vascular remodeling	Sinusoidal capillarization ↓nutrient/ waste exchange	Liver (Mouse)	C57BL/6 Tac Mice (In vivo and ex vivo liver sinusoidal endothelial cells [SECs])	In vivo: 250 ppb sodium arsenite (5 wk) Ex vivo: 8 hr	(Straub et al., 2008)
Endocrine signaling changes	↑fasting serum glucose ↑blood insulin	Pancreas (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/90 days)	(Izquierdo-Vega et al., 2006)
Individual Responses					
Diabetes (Inferred from insulin resistance)	Insulin resistance	Blood (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/ 90 days)	(Izquierdo-Vega et al., 2006)
Liver disease	Hepatic fibrosis	Liver (Mouse)	BALB/c Mice (Male)	3.2 mg/L (15 months)	(Santra et al., 2000) Reviewed in (Flora, 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
Non-malignant respiratory disease	Allergic lung inflammation	Lung (Mouse)	Mice (unspecified strain; wild type and Nrf2-knockout)	0.48 mg/m^3 synthetic dust [10% arsenic trioxide + inert background dust] (30 min/day /14 days)	(Zheng et al., 2012)
Susceptible individual response					
KEAP1 and/or NRF2 mutations	↑ NRF2 activity in skin cancer patients	Skin	Human population	Not applicable	(Kim et al., 2010) cited in (Zhao et al., 2012)
NADPH oxidase p22 subunit polymorphisms	↑hypertension risk in individuals with polymorphisms & high inorganic arsenic exposure	Cardio-vascular system	Human population	0.7 – 0.93 mg/L median inorganic arsenic in well water (>6 months)	(Hsueh et al., 2005); Cited in (Straub et al., 2008)
Diabetics	↓thioredoxin reductase (TrxR)	Pancreas (Rat)	Wistar Rats (Male)	1.7 mg/kg $NaAs^{+3}O_2$ (every 12 hr/ 90 days)	(Izquierdo-Vega et al., 2006); Schulze et al. (2004)
Alcohol	Ethanol may augment oxidative stress and induction of angiogenic factors that would promote tumor growth	Cardiovascular system	Human microvascular endothelial (HMVEC) cells	1-5uM arsenite in presence or absence of 0.1% EtOH. 24 hour experiments	(Klei and Barchowsky, 2008)
Population Response[a]					
Elevated oxidative stress	↑superoxide in plasma (chemiluminescence method) ↓Plasma antioxidants	Plasma (Human)	Human Population (Taiwan)	9.60 µg/L Average arsenic blood levels (Average age: 64 years)	(Wu et al., 2001)
Elevated oxidative stress	↑serum lipid peroxides ↓non-protein sulfhydryl levels in whole blood	Blood (Human)	Human population (Inner Mongolia, China,)	0.41 mg/L Average arsenic blood levels (average: 18 years)	(Pi et al., 2002)
Cardiovascular disease	Peripheral vascular disease, ischemic heart disease, acute myocardial infarction, atherosclerosis, hypertension	Cardiovascular system	Human population	Varies	Cited by (Straub et al., 2008) Reviewed in (Flora, 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References
Bladder cancer	Elevated incidence of bladder cancer in populations exposed to relatively high inorganic arsenic concentrations (>100 µg/L in drinking water)	Bladder	Human population	Varies but generally >100 µg/L in drinking water	Reviewed in (Cohen et al., 2013)
Diabetes	Multiple measures (e.g., insulin resistance)	Endocrine system	Human population	Various	(Maull et al., 2012); cited in (Fu et al., 2010)
Liver Cancer	↑serum Epidermal Growth Factor Receptor in liver cancer patients	Serum	Human Case Controls	Average 0.5 -0.6 mg/L inorganic arsenic in drinking water	(Sung et al., 2012)
Liver disease	Portal hypertension, noncirrhotic liver fibrosis	Liver	Human population	Various	Cited in (Straub et al., 2008)
	Hepatic fibrosis, portal hypertension	Liver	Human population	Various	(Santra et al., 1999); Reviewed in (Flora, 2011)
Lung Cancer	Inferred from EGFR activation in BEAS cells and ↑EGFR in serum of liver cancer patients	Lung	Human population	Various	(Sung et al., 2012; Wu et al., 1999)
Neurotoxicity	Peripheral neuropathy	Nervous system	Human population	Various	Cited by (Rao and Avani, 2004)
Non-malignant respiratory disease	Allergic lung inflammation	Lung	Human population	Various	Cited in (Zheng et al., 2012)
Pregnancy outcomes	preeclampsia, pre-term birth, chorioamnionitis, brain white matter damage, chronic lung disease in preterm infants	Placenta (Human)	Human population	Various	Cited in (Ahmed et al., 2011)
Renal disease	Urinary cancer Renal insufficiency, necrosis, failure	Kidney	Human population	Various	Reviewed in (Flora, 2011)
Skin Disease (Bowmen's Disease, cancer)	↑oxidative DNA adducts (8-OHdG) ↑skin lesions	Skin	Human population	Various	(Pei et al., 2013) Reviewed in (Yu et al., 2006)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)	References

[a]Note: Associations between disease in populations exposed to inorganic arsenic and oxidative stress relies primarily on observational population studies combined with indicators of oxidative stress in in vitro and/or in vivo studies in cell or tissue types relevant to the disease (e.g., cardiomyocytes for cardiovascular disease). Data directly linking inorganic arsenic exposure to disease through an oxidative stress MOA were not identified at the population level, although biomarkers of oxidative stress in populations exposed to inorganic arsenic have been identified.

10.6 Preliminary Data on Potential Interactions between Inorganic Arsenic Exposure and Other Chemicals or Stressors

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
Susceptible Individuals					
Smoking	Multiple epidemiological studies have found smoking interacts with inorganic arsenic exposure to increase lung and bladder cancer risk	Lung Urinary bladder (Human)	Human Population	Variable	(Cohen et al., 2013) review
	Synergistic interaction of smoking andinorganic arsenic ingestion with skin lesions	Skin (Human)	Human population	Variable	(Chen et al., 2006a); (Melkonian et al., 2011)
	Synergistic interaction between inorganic arsenic exposure and smoking in mortality from heart disease	Heart disease (Human)	Bangladesh	25.3-114 ppb	(Chen et al., 2011b)
	Interaction between smoking and bladder-cancer risk (↑ odds ratio in ever smokers compared to never smokers; greater ↑ in odds ratio for smokers with shorter duration of As exposure compared to smokers with longer exposure duration)	Bladder (Human)	Human population (New Hampshire)	>0.330 µg/g toenail As conc. (Inorganic arsenic: 16.5 yrs [average]; Smoking: <15 yrs or ≤ 15 yrs)	(Karagas et al., 2004)
Co-exposures	Synergistic effects between fertilizer use and inorganic arsenic levels in drinking water for skin lesions; longer duration of fertilizer use associated with higher hazard ratio	Skin (Human)	Human population (Bangladesh)	>50 µg/L total arsenic in water (As: 10 yrs [mean]; Fertilizer: <10 yrs) >10 µg/L total arsenic in water (As: 10 yrs [mean]; Fertilizer: >10 yrs)	(Melkonian et al., 2011)

Key Events	Observations	Organ system	Test System	Dose (Exposure Duration)[a]	References
	Cd and As have cumulative effects on renal tubule leakage	Kidney	Humans	Mean concentration of Cd: 1.21.ppb and As: 5.7ppb	(Huang et al., 2009a)
Diet	Low vegetable fiber, low calcium, low folate and low animal protein may increase risk of skin lesions	Skin (Human)	Human Population (West Bengal, India)	<500 µg/L total arsenic (unspecified)	(Mitra et al., 2004)
	Poor nutritional status (low body weight) associated with increased risk of skin lesions	Skin (Human)	Human Population (West Bengal, India)	<73.0 µg/kg/day total arsenic (unspecified)	(Mazumder et al., 1998)
	Lower body-mass index associated with increased risk of skin lesions	Skin (Human)	Human Population (Bangladesh)	Variable	(Milton et al., 2004); (Ahsan et al., 2006)
	Lower dietary intake of folate and other B vitamins led to a stronger positive association between exposure and hypertension	Hypertension (Human)	Human population (Bangladesh)	<864 ppb	(Chen et al., 2007b)
	Development of skin lesions associated with low folate	Skin/Blood (human)	Peripheral blood lymphocyte DNA in individuals with skin lesions	2-250 µg/L As(III) (>2 years)	(Pilsner et al., 2009)
	Non-toxic inorganic arsenic exposure leads to enhanced inorganic arsenic accumulation when combined with Se-deficiency; could affect fetal brain development	Brain (Developing Mouse)	Pregnant ICR mice	58 µmol/kg/day sodium arsenite +/-Se-deficient diet	(Miyazaki et al., 2005)

10.7References for Mode of Action Hypothesis Summaries and Preliminary Adverse Outcome Pathway Tables

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