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IRIS Toxicological Review of Inorganic Arsenic

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ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDU	benchmark dose upper confidence limit
BML	benchmark concentration lower confidence limit
BMCU	benchmark concentration upper confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DCS	diseases of the circulatory system
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DMA	dimethylarsinic acid
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
HAWC	Health Assessment Workspace Collaborative
Hb/g-A	animal blood: gas partition coefficient
Hb/g-H	human blood: gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
HERO	Health and Environmental Research Online
IARC	International Agency for Research on Cancer
iAs	inorganic arsenic
i.p.	intraperitoneal
IPCS	International Program on Chemical Safety
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MMA	monomethylarsonic acid
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
RRB	relative risk over the background exposure
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid

TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_H	human variation uncertainty factor
UF_L	LOAEL-to-NOAEL uncertain factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database deficiencies uncertainty factor
U.S.	United States

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EXECUTIVE SUMMARY

ES.1 SUMMARY OF OCCURRENCE AND HEALTH EFFECTS

Inorganic arsenic (iAs, CASRN 7440-38-2) is a naturally occurring compound that can be found in water, food, soil, and air. In addition, arsenic can be released into the environment through industrial processes and emissions. Arsenic is used in paints, dyes, metals, drugs, soaps, semiconductors, and, to a limited extent, in wood preservatives (i.e., commercial, and marine applications). Agricultural applications, mining, and smelting also contribute to arsenic releases in the environment. Arsenic is an odorless and tasteless chemical that can enter drinking water, food supplies, soil, and air from natural deposits in the earth or from agricultural and industrial practices. As such, exposure is possible via ingestion of drinking water and food, inhalation of air, and dermal contact.

The Integrated Risk Information System (IRIS) Program is developing this assessment of iAs at the request of multiple EPA National and Regional Programs. The methods used in the assessment are summarized in the iAs Protocol (link provided in Appendix A) and have been reviewed by the National Academies of Sciences, Engineering, and Medicine (NASEM; formerly the National Research Council) (NRC, 2013). Methods and problem formulation decisions were heavily informed by prior NASEM input (NRC, 2014; NASEM, 2019). This Toxicological Review updates the prior IRIS assessment (U.S. EPA, 1995). Scoping and problem formulation for this assessment drew extensively on assessments conducted by others (WHO, 2000, 2011a, b; U.S. EPA, 2002a; NTP, 2016; IARC, 2004a, 2012; FDA, 2005; ATSDR, 2007).

Human epidemiological studies have identified a number of associations between iAs exposure and cancer and noncancer health outcomes (NRC, 2013). As described in the iAs protocol (link provided in Appendix A), skin, bladder, and lung cancer and skin lesions are accepted hazard outcomes for iAs based on previous assessments by EPA and other health agencies. EPA has classified arsenic as ***carcinogenic to humans*** based on epidemiological evidence (U.S. EPA, 1995), and that classification is retained in the current assessment (U.S. EPA, 2005a). For these outcomes, the focus of this assessment is to update quantitative estimates of cancer risk. In the current assessment new evidence synthesis and judgment conclusions were developed for noncancer effects of the circulatory system, fetal, newborn, and infant health outcomes, neurodevelopmental effects, and diabetes based on the review of the available epidemiological evidence, as recommended, and supported by the NASEM (NRC, 2013; NASEM, 2019).

On the basis of a *robust* epidemiological evidence base, the currently available **evidence demonstrates** that iAs causes diseases of the circulatory system (DCS) and diabetes in humans given sufficient exposure conditions. *Robust* evidence from humans leads to the strongest evidence integration conclusion of **evidence demonstrates** (U.S. EPA, 2020). For diseases of the circulatory

system, the primary support for this hazard conclusion included evidence of increased ischemic heart disease (IHD) and hypertension, as well as related cardiovascular disease endpoints of atherosclerosis and repolarization abnormalities (e.g., QT prolongation). For diabetes, the primary supporting evidence included increased incidence of type 2 diabetes mellitus. Quantitative estimates were derived for these two noncancer hazards and used to identify a reference dose (RfD).

An evidence synthesis judgment of *moderate* was reached for fetal, newborn, and infant health outcomes and neurodevelopmental effects, and the currently available **evidence indicates** that inorganic arsenic likely causes fetal, newborn, and infant health outcomes and neurodevelopmental effects in humans given sufficient exposure conditions. For fetal, newborn, and infant health outcomes, the primary supporting evidence for this hazard conclusion included increased fetal and infant mortality, inverse fetal and post-natal growth, length of gestation or birth weight. For neurodevelopmental effects, the primary supporting evidence included cognitive and behavioral deficits in children and adolescents. An RfD was derived for fetal, newborn, developmental neurocognitive, and infant health outcomes.Table ES-1 summarizes the organ/system-specific RfDs derived for the health outcomes.

ES.2 TOXICITY VALUES FOR NONCANCER AND CANCER EFFECTS

Presentation of traditional, noncancer toxicity values (i.e., the RfD and osRfDs) as well as probabilistic toxicity values (i.e., risk-at-a-dose values) allows users of the iAs assessment to estimate lifetime extra risk for individual endpoints at different iAs exposure levels (e.g., several-fold above the final RfD), noting that the definition of the RfD is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." Both the traditional and probabilistic toxicity values are useful within specific decision contexts. Modeling results are discussed throughout Section 4. Presenting a traditional RfD is important because certain decisions made by EPA rely on the use of such a value given statutory requirements. Probabilistic methods are also useful, for example in cost benefit analyses. However, development of traditional and probabilistic values involves different assumptions, methods, and uncertainties. These differences would be considered, dependent on context, during development of subsequent risk assessments by EPA or others.

For noncancer effects, candidate RfD toxicity values of 0.058 μg/kg-day and 0.057 μg/kg-day were estimated for IHD and diabetes, respectively, using the Bayesian dose-response meta-analysis approach described in Sections 4.3.7 and 4.3.8 (see Table ES-1). For fetal, newborn, and infant health outcomes (decreased birth weight) and developmental neurocognitive effects, candidate RfD toxicity values of 0.079 μg/kg-day and 0.105 μg/kg-day were estimated using the methods described in Sections 4.4 and 4.5. Overall, an RfD of **0.06 μg/kg-day (rounded to one significant digit) based on increased incidence of diabetes and IHD in humans** was selected. Confidence in the RfD is *medium-high*, based on *high* confidence in the diabetes organ/system-

specific RfD and *medium-high* confidence in the IHD organ/system-specific RfD. While the IHD organ/system-specific RfD is based on the lowest POD_{HED} using a dose-response meta-analysis approach that included *high* and *medium* confidence studies (0.171 μg/kg-day, compared with 0.174 μg/kg-day for diabetes), rounding the resulting organ-specific RfDs to one significant digit results in identical values (i.e., 0.06 μg/kg-day). The final RfD is expected to be protective against all noncancer adverse health effects associated with iAs and across all life stages. The decision to base the final RfD on both IHD and diabetes was based on all available organ-specific RfDs in addition to overall confidence and composite uncertainty for those RfDs.

Table ES-1. Toxicity values for noncancer outcomes associated with inorganic arsenic exposure

Health outcome	Hazard descriptor	$BMDL_{05}$ (μg/kg-d)	UF_C	RfD (μg/kg-d)	Confidence in RfD
Diabetes	Evidence demonstrates	0.174[a]	3	0.058	*High*
IHD		0.171[a]	3	0.057	*Medium-high*
Fetal, newborn, and infant health outcomes	Evidence indicates (likely)	0.237[b]	3	0.079	*Medium*
Developmental neurocognitive		0.315[b]	3	0.105	*Medium*
Overall RfD	–	–	–	**0.06**	*Medium-High*

[a]BMDL estimated as the 95th percent lower bound of the BMD posterior distribution calculated using the dose-response meta-analysis logistic slope and power parameters.

[b]The fetal, newborn, and infant health outcome and developmental neurocognitive PODs are BMDLs calculated as described in Sections 4.4 and 4.5.

Mean lifetime extra risks of 7.9 and 10.1 were estimated for bladder cancer and lung cancer, respectively, for a hypothetical U.S. cohort of 10,000 individuals[1] exposed for a lifetime at the U.S. drinking water standard of 10 μg/L. The cancer slope factors (CSF) provided for bladder cancer and lung cancer in Table ES-2 represent the slope of the linear trendline between the estimated 95% upper bound on lifetime extra risk and dose, from zero dose to 0.2 μg/L. These CSF values can be multiplied by other estimates of lifetime μg/kg-day dose to estimate the 95% upper bound on lifetime extra risk for the endpoint in question. As noted in Table ES-2 (footnote b), these cancer slope factors are estimated from the risk estimates in the low-dose region (corresponding to <0.2 μg/kg-day for bladder and lung cancer), which displays an approximately linear dose-response relationship. Above that dose level, the relationship becomes increasingly nonlinear and risk estimates should not be obtained using the CSF. Instead, at higher doses, the polynomial equations

[1]Additional cases in a cohort of size N for extra risk, x, when the background rate is b, is equal to N × (1-b) × x (see Section 4.3.4 for the estimated U.S. lifetime health effect background rates).

in Figure 4-6 and Figure 4-7 should be used. A combined cancer slope factor of 3.17×10^{-2} $(\mu g/kg\text{-}day)^{-1}$ (valid for daily intakes less than 0.2 µg/kg-d) was also estimated according to the method described in footnote c of Table ES-2.

Table ES-2. Toxicity values for cancer outcomes associated with inorganic arsenic exposure

Health Outcome	Hazard Descriptor	Cancer Slope factor (CSF) 1/(µg/kg-d)[a, b, c]
Bladder cancer	Carcinogenic to humans	1.76×10^{-2}
Lung cancer		2.13×10^{-2}
Combined cancer risk[d]		3.17×10^{-2}

[a]Estimate of the 95% upper-bound lifetime extra risk per µg/kg – day oral dose above an estimate of risk at zero dose, assuming U.S. background risks are associated with a U.S. background dose of 0.0365 µg/kg, which includes 0.02 µg/kg – day from diet, 0.0165 µg/kg – day from water and 0 µg/kg – day from air (see Section 4.3.4).

[b]EPA estimates of lifetime extra risk per µg/kg-day dose above background is increasingly nonlinear above 0.2 µg/kg-day for bladder (see Section 4.3.5) and lung (see Section 4.3.6) cancer. For these health outcomes, risk estimates in the nonlinear region should not be obtained from the CSF, but from the nonlinear polynomial equations provided in those sections.

[c]Cancer slope factors in units of $(mg/kg\text{-}day)^{-1}$ are 17.6 $(mg/kg\text{-}day)^{-1}$, 21.3 $(mg/kg\text{-}day)^{-1}$, and 31.7 $(mg/kg\text{-}day)^{-1}$ for bladder cancer, lung cancer, and combined risk, respectively.

[d]Calculated as described in the Toxicological Review of Chloroprene (U.S. EPA, 2010), assuming a normal distribution and using MLE and 95% upper-bound linear slope estimates shown in Figure 4-6 (bladder cancer) and Figure 4-7 (lung cancer). The combined CSF is calculated as $\sum(MLE\ slopes) + 1.645 \times composite\ SD$. The composite SD equals $\sqrt{\sum variances} = \sqrt{\sum\left(\frac{upper\ bound - MLE}{1.645}\right)^2} = \sqrt{\left(\frac{0.0176-0.0062}{1.645}\right)^2 + \left(\frac{0.0213-0.0078}{1.645}\right)^2} = 0.0107$. Thus, the combined CSF equals $(0.0062 + 0.0078) + (1.645 * 0.0107) = 0.0317$.

For the non-cancer endpoints, mean lifetime extra risks of 110 and 129 were estimated for IHD and diabetes, respectively, for a hypothetical U.S. cohort of 10,000 individuals exposed for a lifetime at the U.S. drinking water standard of 10 µg/L. Table 4-10 in Section 4.3.10 compares the mean and upper-bound lifetime extra risks for bladder cancer, lung cancer, IHD, and diabetes at the current drinking water standard of 10 µg/L, along with the various linear and polynomial trendlines calculated for each endpoint. See Sections 4.3.5 (bladder cancer), 4.3.6 (lung cancer), 4.3.7 (IHD), and 4.3.8 (diabetes) for full presentation of lifetime extra risks across a wide range of daily intake values. These endpoint-specific sections provide calculated lifetime risks for the modeled endpoints across a range of daily intakes up to 1.0 µg/kg-day. Linear and/or polynomial trendline equations that provide approximations of the calculated lifetime extra risks are also provided. Endpoint-specific tables in Appendix C (Tables C-31, C-41, C-49, and C-59) provide lifetable-calculated risks up to 1.5 µg/kg-day at increments of 0.005 µg/kg-day. Users that need to generate exact mean or upper-bound lifetime extra risk values at daily intakes other than those reported in the appendix tables can use the Bayesian logistic-power modeling results and lifetable

R codes (U.S. EPA, 2025). See the structured workflow, outline, and variable dictionary (U.S. EPA, 2024b) for documentation of modeling files.

The risk estimates from EPA's dose-response meta-analyses of bladder cancer, lung cancer, diseases of the circulatory system (IHD), and diabetes represent predicted lifetime extra risk above a zero dose. To estimate the risk at zero dose, U.S. lifetime background risks reported in CDC lifetables or sourced from the literature are assumed to be associated with an iAs U.S. background dose of 0.0365 μg iAs/kg-day (from dietary and drinking water sources).[2] As discussed in the Section 4.3 (Bayesian dose-response meta-analysis), sensitivity analyses indicate that inhalation exposures would not have a significant impact on lifetime extra risk estimates. Therefore, risk estimates for oral exposures are calculated assuming zero inhalation exposure. The bladder cancer, lung cancer, DCS, and diabetes dose-response meta-analyses include studies with total iAs daily intake and iAs drinking water exposure levels in the range of U.S. levels, predominantly <1 μg/kg-day to 100 μg/L. Studies were not excluded from dose-response analyses, if they included both low- to moderate exposure groups (i.e., <100 μg/L) and higher exposure groups (i.e., >100 μg/L), provided they met all other study inclusion criteria.

[2]See Section 4.3.4 for a discussion of how these U.S. background rates, and this U.S. background dose were estimated.

1. BACKGROUND INFORMATION AND ASSESSMENT METHODS

1.1. INTRODUCTION

The inorganic arsenic assessment (iAs) is being developed by the Integrated Risk Information System (IRIS) Program at the request of U.S. Environmental Protection Agency's (EPA) Office of Land and Emergency Management (OLEM), Office of Water (OW), and regions 1–10 (see December 2018 IRIS Program Outlook). This assessment evaluates the publicly available studies on iAs in order to identify its adverse health effects and to characterize exposure-response relationships. In addition to use by OLEM and OW, this assessment can be used by other EPA National Program and Regional offices, states and local health agencies, Tribes, other federal agencies, international health organizations, and other external stakeholders.

A link to the updated problem formulation and systematic review protocol for the iAs assessment is contained in Appendix A. The protocol outlines the updated scoping and problem formulation efforts relating to this assessment. The protocol also lays out the systematic review and dose-response methods used to conduct this review. This updated problem formulation and systematic review protocol was released in 2019 for public comment and review by NASEM (2019). NASEM recommendations and public comments were considered in preparing the draft assessment and protocol amendments (see Protocol, Section 6, for a description of the amendments).

This assessment was released for public comment on October 16, 2023, and comments were due on December 16, 2023. BMD Model Code and Modeling Results were released for public comment on December 29, 2023, and comments were due January 16, 2024. The public comments are available on Regulations.gov in Docket EPA-HQ-ORD-2012-0830. A summary and EPA's disposition of the comments received is included in Appendix F. This assessment was peer reviewed by independent expert scientists external to EPA convened by the EPA Science Advisory Board (SAB). Peer-review meetings were held on January 5, 2024; January 24–26, 2024; July 8, 2024; July 16, 2024; and October 15–16, 2024. The report of the review of the EPA's Draft Toxicological Review of Inorganic Arsenic, dated November 19, 2024, is available on the IRIS website. A summary and EPA's disposition of the comments received is included in Appendix F.

1.2. BACKGROUND INFORMATION ON INORGANIC ARSENIC

Section 1 provides a brief overview of aspects of the physicochemical properties; sources, production, and use; environmental fate and transport; and human exposure characteristics of inorganic arsenic (iAs, CASRN 7440-38-2). This overview is not intended to provide a

comprehensive description of the available information on these topics but to provide contextual information for the assessment.

1.3. PHYSICAL AND CHEMICAL PROPERTIES

Elemental arsenic, or metallic arsenic, is a steel grey solid with chemical and physical properties intermediate between a metal and nonmetal (IARC, 2009). Arsenic can exist in four oxidation states: −3, 0, +3, or +5. Because of its reactivity, elemental arsenic (oxidation state 0) is rarely found in the environment (U.S. EPA, 2006; ATSDR, 2007). Instead, arsenic is often found combined with other elements and commonly exists in biologic systems as: arsenite ($AsIIIO_3^{-3}$), arsenate ($AsvO_4^{-3}$), arsenide (As^{-3}), and organic arsenic compounds (As-C covalent bond). The IRIS assessment is limited to inorganic arsenic, defined as arsenite and arsenate salts and arsenoxides. For the purposes of this document, the term arsenic refers to inorganic arsenic unless otherwise specified. Arsenate and arsenite compounds and alkylated arsenic species are used commercially. Inorganic arsenic predominates in environmental media (air, water, soil) and commercial uses and it is more toxic than organic arsenic (U.S. EPA, 2006; OEHHA, 1996; ATSDR, 2007). The chemical and physical properties of arsenic are listed in Table 1-1.

Table 1-1. Chemical and physical properties of arsenic and selected inorganic arsenic compounds (ATSDR, 2000; Budavari, 1989)

	Arsenic	As_2O_3	As_2O_5	$NaAsO_2$	Na_2HasO_4
CAS No.	7440-38-2	1327-53-3	1303-28-2	7784-46-5	7778-43-0
Oxidation state	0	+3	+5	+3	+5
Molecular weight	74.9	197.8	229.8	129.9	185.9
Synonyms	Metallic arsenic, grey arsenic	Arsenic trioxide, arsenolite, white arsenic (+3)	Arsenic pentoxide, arsenic acid anhydride (+5)	Sodium arsenite (+3)	Disodium arsenate (+5)
Physical state (25°C)	Solid	Solid	Solid	Solid	Solid
Boiling point (°C)	613 (sublimes)	465	–	–	–
Melting point (°C)	817 @ 28 atm	312	315 (decompose)	–	86.3
Density (g/cm^3)	5.7	3.7	4.3	1.8	1.8

– No data available.

1.4. SOURCES, PRODUCTION, AND USE

Inorganic arsenic is widely distributed throughout the Earth's crust and is present in more than 200 mineral species (IARC, 2009; Health Canada, 2006; ATSDR, 2007). 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 (IARC, 2012).

Inorganic arsenicals are used in the manufacturing and processing of several products. The arsenic metalloid is used for hardening copper and lead alloys (HSDB, 2005). It is also used in glass manufacturing as a decolorizing and refining agent, as a component of electrical devices in the semiconductor industry, and as a catalyst in the production of ethylene oxide. Arsenic compounds are used as a mordant in the textile industry, for preserving hides, as medicinals, pesticides, pigments, and wood preservatives. The production of chromate copper arsenate, a wood preservative, accounts for approximately 90% of the domestic arsenic consumption (ATSDR, 2007). However, production of this preservative is being phased out since 2003 (ATSDR, 2007). The uses of inorganic arsenical compounds (e.g., lead arsenate) as pesticides were voluntarily cancelled by the industry during late 1980s and early 1990s. The majority of organoarsenicals are used on cotton and turf as herbicides. Disodium methanearsenate (DSMA), monosodium methanearsenate (MSMA), and calcium methanearsenate (CAMA) continue to be used as contact herbicides.

1.4.1. Environmental Fate and Transport: Soil

In soil there are many biotic and abiotic processes controlling arsenic's overall fate and environmental impact. Arsenic in soil exists in various oxidation states and chemical species, depending upon the soil pH and oxidation-reduction potential (ATSDR, 2007). Arsenic is largely immobile in agricultural soils and tends to remain in upper soil layers (ATSDR, 2007). However, reducing conditions form soluble mobile forms of arsenic and leaching is greater in sandy soil than in clay loam (ATSDR, 2007). Mobility of arsenicals is typically very low to intermediate, and sorption is higher in soils with higher percentage of clay or with more iron or aluminum content (U.S. EPA, 2006).

1.4.2. Environmental Fate and Transport: Water

Transport and partitioning of arsenic in water depends upon the chemical form of the arsenic and on interactions with other materials present (ATSDR, 2007). Under normal conditions in water, arsenic is present as soluble inorganic As^{V} because it is thermodynamically more stable in water than As^{III}. Soluble forms may be carried long distances through rivers, but arsenic may also be adsorbed from water onto sediments or soils, especially clays, iron oxides, aluminum hydroxides, manganese compounds, and organic material (Welch et al., 1988; U.S. EPA, 1982). Groundwater arsenic concentrations are usually controlled by adsorption rather than by mineral precipitation under oxidizing and mildly reducing conditions (ATSDR, 2007).

1.4.3. Environmental Fate and Transport: Air

High temperature processes, such as coal and oil combustion, smelting operations, and refuse incineration, contribute to most of the anthropogenic arsenic emitted to the atmosphere (Pacyna, 1987). These fine particles, with a mass median diameter of about 1 μm, can reside in the atmosphere for about 7–9 days and be transported thousands of kilometers by wind and air currents until they are returned to earth by wet or dry deposition (Pacyna, 1987). Atmospheric fallout can also be a significant source of arsenic in coastal and inland waters near industrial areas (ATSDR, 2007).

1.5. OCCURRENCE IN THE ENVIRONMENT

Arsenic naturally comprises ~ 3.4 parts per million (ppm) of the earth's crust, where it is the twentieth most abundant element (ATSDR, 2007). Arsenic leaches from natural weathering of soil and rock into water and low concentrations of arsenic are found in water, food, soil, and air. However, industrial activities such as coal combustion and smelting operations release higher concentrations of arsenic to the environment (Adams et al., 1994). The highest background arsenic levels found in the environment are in soils, with concentrations ranging from 1 to 40 ppm (ATSDR, 2007). Food typically contains total arsenic concentrations of 20 to 140 parts per billion (ppb), with inorganic arsenic levels being much lower than organic arsenic levels (ATSDR, 2007). The majority of surface and ground waters contain less than 10 μg/L[3] (although levels of 1,000–3,400 μg/L have been reported, especially in areas of the western United States) (DeSimone et al., 2015; ATSDR, 2000). The average arsenic content in drinking water in the United States (U.S.) has been estimated to be 2 μg/L with approximately 12% of the water supply from surface water in central portions of the U.S. and 12% of groundwater sources in western portions of the U.S. exceeding 20 μg/L (DeSimone et al., 2015; ATSDR, 2007). Mean arsenic concentrations in ambient air have generally been found to range from 1 to 2,000 ng/m^3 (Wai et al., 2016; ATSDR, 2007).

1.5.1. Potential for Human Exposure and Populations with Potentially Greater Exposure

Oral exposure is the primary route of environmental exposure to inorganic arsenic, occurring through dietary intake of contaminated food or drinking arsenic-contaminated water. This assessment focuses on oral exposure based on agency needs.

Inorganic arsenic is found in meats, poultry, dairy products, and cereal (IARC, 2009). High levels of inorganic arsenic have been found in rice cereals Signes-Pastor et al. (2016) and rice cereal is the largest source of inorganic arsenic for four- to 24-month-olds Shibata et al. (2016). Elevated exposures to arsenic from rice products and other foods commonly consumed by infants during to the transition to solid foods represents an important source of exposure during a critical window of development (Signes-Pastor et al., 2018). Inorganic arsenic has also been found in fruit juices and

[3]For water concentrations, 1 μg/L = 1 ppb.

infant rice cereal and the FDA currently recommends an "action level" of 10 ppb for inorganic arsenic in apple juice (FDA, 2013) and 100 ppb in infant rice cereal (FDA, 2016; FDA, 2020). In young children, oral exposure to inorganic arsenic may also 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, especially rice and rice-derived sweeteners used in organic food products, grown in soil containing inorganic arsenic have been shown to concentrate arsenic (Jackson et al., 2012; Pogoson et al., 2021).

During early life, inorganic arsenic and its methylated metabolites readily pass the placental barrier, resulting in potentially elevated fetal exposure (Vahter, 2009; Hall et al., 2007; Concha et al., 1998). With advancing gestation, the efficiency of maternal arsenic methylation increases, resulting in lower exposure of the fetus to inorganic arsenic and MMA (Vahter, 2009; Li et al., 2008; Gardner et al., 2011; Concha et al., 1998). However, if maternal exposure is high, maternal arsenic methylation could be inhibited, resulting in elevated exposure of the fetus to inorganic arsenic and MMA (Vahter, 2009). The transfer of arsenic into breast milk is limited, and breastfeeding, which results in efficient methylation of arsenic and contains choline, antioxidants, and other protective components, can partially shield infants from some of the adverse impacts of arsenic exposure (Vahter, 2009; Fängström et al., 2008; Concha et al., 1998). However, formula-fed infants experience elevated exposure due to the inorganic arsenic content of formula powder as well as arsenic-contaminated drinking water used for reconstitution (Carignan et al., 2015).

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, the 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 (DeSimone et al., 2015; ATSDR, 2007).

Some studies in this assessment were conducted in areas with fairly high levels of arsenic contamination in groundwater while others cover populations with lower levels of potential exposure. However, not all epidemiological studies cited in this assessment clearly report external exposure levels in environmental media for the populations under investigation and therefore it is not feasible to contextualize all studies with respect to environmental exposure levels. To help provide context, Figure 1-1 illustrates historical exposure levels across the world (Schwarzenbach et al., 2010). In Section 3.2, the country where each epidemiology study was conducted is presented

in data visualizations (i.e., forest plots) to provide information on relative environmental exposure levels. For summary purposes, higher exposures are considered to be from countries such as Bangladesh, China, and Chile, while lower exposures include the United States, Mexico, and Denmark. Supplemental pivots for for scenarios with maximum arsenic exposures <100 µg/L in drinking waterare described in 1.6.3 below.

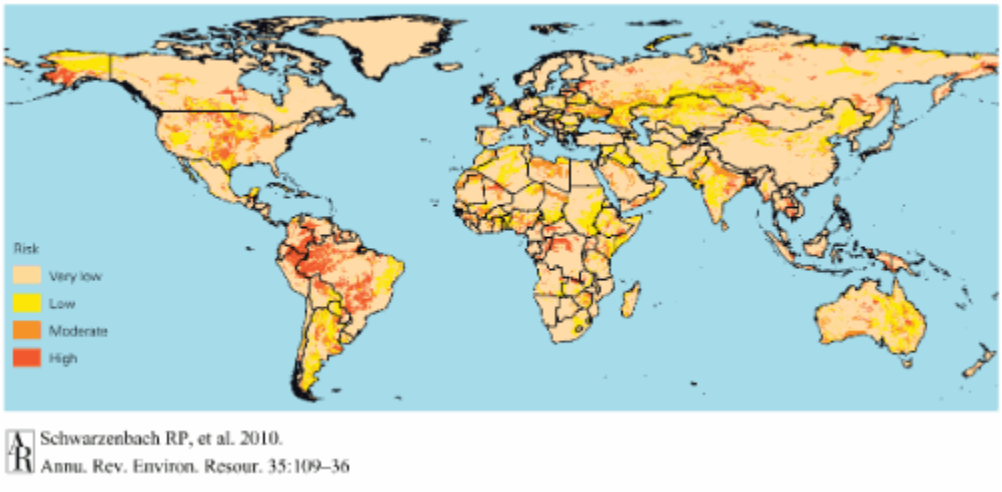


Figure 1-1. Arsenic levels in groundwater across the world (Schwarzenbach et al., 2010).

Source: https://pubs.acs.org/doi/10.1021/es702859e. Further permissions related to the figure should be directed to the ACS.

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 (WHO, 2000). Higher levels of inhalation exposure to inorganic arsenic are observed in more "polluted" areas, include areas near smelting, coal-fired power plants, pressure-treated wood, glass manufacturing, and electronics industry. Both direct inhalation and consumption and inhalation of re-entrained dust can be of concern. WHO (2000) reports that near emission sources concentrations of airborne arsenic can exceed 1 µg/m^3. Smokers can be exposed up to 10 µg/day of arsenic due to the natural absorption of arsenic from soil by tobacco plants (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). Since oral exposure is the primary route of exposure for the general population, inhalation exposure to inorganic arsenic was not evaluated further in the main analysis. However, the impact consideration of inhalation exposure has on risk estimation was investigated in sensitivity analyses (Appendix C.1.2). In addition, the primary agency need is oral,

inhalation studies are mainly occupational studies, and the bulk of the new epidemiological studies concern oral exposure.

Dermal exposure is a potential route of exposure for inorganic arsenic, but it is generally accompanied by either inhalation or oral exposure; either of which would be the more predominant exposure route. Inorganic arsenic is found in soils, but due to the formation of insoluble complexes with iron, aluminum, or magnesium oxide, it is poorly absorbed in humans (ATSDR, 2007). Exposure through bathing in contaminated water is a possibility and may contribute to effects, but there are no studies to quantify the dermal exposure. Dermal exposure may play a larger part in effects to the skin. In vitro studies using artificial human skin indicates that the skin would retain 1%–10% of the applied dose (Bernstam et al., 2002). Although dermal exposure may add to the overall exposure, it is not a focus of this assessment because it represents minimal exposure compared with oral or inhalation exposure, that there are no studies that specifically evaluate effects after dermal exposure, and that there are no physiologically based pharmacokinetic (PBPK) models in humans to convert from oral to dermal exposure precludes consideration of dermal exposure in this assessment.

1.6. SUMMARY OF ASSESSMENT METHODS

Section 1.6 summarizes the methods used for developing this assessment. As outlined in the *Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment* (link provided in Appendix A), epidemiological evidence is the focus of this assessment given the abundance of epidemiological evidence and preference for using human data over animal data when available (NRC, 2013; NASEM, 2019). With respect to the animal data, most adult laboratory animal models appear to be less susceptible to inorganic arsenic than humans when comparative information is available (Vahter and Norin, 1980; Vahter, 1994; Lynch et al., 2017a, b). Interspecies metabolism differences likely explain the differences in toxicity between animals and humans, with animals requiring higher doses to reach internal doses comparable to those observed in humans. Thus, analysis of the epidemiological evidence base was the basis for prioritizing health outcomes for dose-response analysis. Mechanistic evidence has also been extensively considered during the course of preparing this assessment, especially in the context of addressing differences in anticipated response among humans (e.g., between children and adults) and to inform decisions about the anticipated shape of the dose-response relationship. Ultimately, the epidemiological evidence was comprehensive and sufficient to inform these judgments. This approach was supported by the NRC (2013) and NASEM (2019), and is consistent with assessments by others (TCEQ, 2017; EFSA, 2009; ATSDR, 2007).

1.6.1. Literature Search and Screening

The detailed search approach, including the query strings are provided in Section 3.3 and Appendix B of the protocol. Populations, Exposures, Comparators, and Outcomes (PECO) criteria

(see Table 1-2) were used to identify the evidence that addresses the specific aims of the assessment and to focus the literature screening, including study inclusion/exclusion. PBPK models are considered to meet PECO criteria. The initial PECO for inorganic arsenic was based on recommendations presented in the 2013 National Research Council *Critical Aspects of EPA's Integrated Risk Information System Assessment of Inorganic Arsenic* (NRC, 2013). Changes in the PECO over time are reflected in Table 1-2, reflecting an ascertained focus on epidemiological studies and prioritized health outcomes (bladder cancer, lung cancer, DCS, diabetes, fetal, newborn, and infant health outcomes, and neurodevelopmental effects) [see Section 3.2 for more details on the focus of these health outcomes and (NASEM, 2019)]. The literature search was first conducted in 2012 and regular updates were performed (see below for additional details). The literature search queries the following databases (no date or language restrictions were applied):

- PubMed (National Library of Medicine)
- Web of Science (Thomson Reuters)
- Toxline (National Library of Medicine)[4]

All literature is tracked in the U.S. EPA Health and Environmental Research Online (HERO) database (https:// https://hero.epa.gov/hero/index.cfm/project/page/project_id/2211).

Table 1-2. Populations, exposures, comparators, and outcomes (PECO) and other inclusion criteria

PECO element	Evidence
Populations	This assessment focuses on human studies only to include any population and life stage (occupational or general population, including children and other sensitive life stages or populations).

[4]Toxline has recently been moved into PubMed as part of a broad National Library of Medicine reorganization. Toxline searches can now be conducted within PubMed.

PECO element	Evidence
Exposures	Subchronic- or chronic -duration studies of interest provide quantitative estimates of exposure with measurements based on biomonitoring data (e.g., hair, nails, urine, or blood), drinking water exposures (µg/L), cumulative exposures (µg/m^3*yr; µg/L*yr), and doses expressed as µg/d and µg/kgd-. Studies with episodic or acute exposures will be excluded (i.e., poisonings or other short term- exposures that last up to 30 d). Studies using arsenicals, primarily arsenic trioxide and Fowler's solution will be excluded because chemotherapeutic agents are not within the scope of this review. Studies using arsenide (As^{3-}), an inorganic form of arsenic, also will be excluded. Exposures usually occur via the gas arsine and result in a different, distinctive toxicological profile based on binding to hemoglobin and red blood cell lysis. This assessment focuses on oral exposure because it is the main route of exposure for the general population, it is a primary agency need, and most inhalation studies are occupational studies.
Comparators	A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of inorganic arsenic, or exposure to inorganic arsenic for shorter periods of time, or cases vs. controls. Exposure-response quantitative results are presented in sufficient detail (e.g., odds ratios or relative risks with associated confidence intervals, numbers of cases/controls).
Outcomes	Health outcomes of interest, based on hazard judgment, relative risk over the background exposure (RRB), and potential use for benefit-costs analysis by program offices, include bladder cancer, lung cancer, DCS, diabetes, fetal, newborn, and infant health outcomes, and neurodevelopmental effects.
Other included study types	
PBPK models	Studies describing PBPK models for inorganic arsenic will be considered to meet PECO criteria.

PBPK = physiologically based pharmacokinetic.
Note: Animal and mechanistic data are considered supplemental material and not tracked as PECO relevant (see Sections 2.3.1. and 2.3.2. of the protocol, Appendix A).

In addition to evaluating studies for adherence to PECO criteria, studies containing supplemental material that did not meet PECO criteria potentially relevant to the specific aims of the assessment were inventoried during the literature screening process. Functionally, supplemental material studies were not excluded. Some studies could emerge as being critically important to the assessment and may need to be evaluated and summarized at the individual study level (e.g., certain cancer MOA or ADME studies), or might be helpful to provide context (e.g., provide hazard evidence from routes or durations of exposure not meeting the assessment PECO), Studies categorized as "potentially relevant supplemental material" included the following:

- Epidemiological studies on other health outcomes not listed in PECO.
- Toxicology: Experimental animal studies presenting original data investigating the effects of chronic exposure to iAs.

- Mode of action/mechanistic: Studies that examine the molecular and/or cellular events and alterations in system biology occurring after iAs exposure (e.g., alterations in epigenomics, genomics, oxidative stress, immune function, and endocrine disruption). Metabolites of iAs are only considered as they pertain to MOA.

- Meta-analyses that contain original analyses.

- Susceptibility: Studies that do not meet PECO-based inclusion criteria, but which include analyses of health effects relevant to the PECO that are evaluated based on potential risk modifiers (e.g., smoking, genetic polymorphisms, susceptibility due to methylation capacity, socioeconomic factors, ethnicity). Studies that identify potentially susceptible subgroups based on intrinsic factors (e.g., age, sex, genetics, health status, behaviors) and certain extrinsic factors (e.g., socioeconomic status, access to health care), studies that identify groups based on extrinsic factors, such as increased risk for exposure due to occupation or residential proximity to exposure sources, are not considered to be susceptible populations.

- ADME/pharmacokinetics (PK): Studies that examine internal dose metrics, absorption, distribution, metabolism, and excretion (i.e., PK).

- Exposure assessment: Studies that describe exposure to arsenic in the air, water, food, or through dermal contact. Includes bioavailability studies for the different media and studies that measured arsenic levels in humans (e.g., in nails, urine, blood) and studies that do not evaluate health outcomes but provide an understanding of arsenic exposures that may be associated with health effects.

The literature was screened by two independent reviewers with a process for conflict resolution, first at the title and abstract level and subsequently the full-text level. Literature inventories for PECO relevant studies and studies tagged as "potentially relevant supplemental material" during screening were created to facilitate subsequent review of individual studies or sets of studies by topic-specific experts.

Literature searches and updates were completed between 2012 and 2019. Following prioritization of the six select outcomes, another literature search was conducted in 2022. The characterization of newly identified studies from the 2022 literature search update focused on EPA's judgment of whether studies would have a material impact on the conclusions (i.e., identified hazards or toxicity values) in the external review draft (see Table B-17 in Appendix B.3).

DCS and diabetes studies identified in the most recent literature search update (August 2022) did not undergo study evaluation because EPA already characterized the strength of the evidence base for these health outcomes to be *robust* (based on studies identified up to 2019) and EPA determined that these new studies would not impact the draft hazard conclusion. However, as discussed in Section 4.3, these studies were considered for dose-response utility and evaluated against criteria of particular importance for EPA's dose-response meta-analysis approach [see the iAs Protocol (link provided in Appendix A), Section 5.1]. For DCS and diabetes, if a study from the recent literature search update made it through study selection for dose-response, it then underwent study evaluation to ensure that it was *medium* or *high* confidence. This allowed EPA to

prioritize efforts for study evaluation focusing on those studies that could be considered suitable for dose-response largely based on study design characteristics (Section 1.6.5).[5]

EPA characterized the strength of the evidence base to be *moderate* for fetal, newborn, and infant health outcomes and neurodevelopmental effects (based on studies identified up to 2019) and studies identified in the 2022 update underwent risk of bias evaluation to determine if new studies would change the hazard conclusion and/or impact dose-response analyses. To further screen studies for dose-response utility, additional consideration was given to study type and whether the study took into account key confounding factors, such as smoking. Studies from the recent literature search update are included in the synthesis sections for fetal, newborn, and infant health outcomes and neurodevelopmental effects. An additional literature search update focusing on neurodevelopmental effects was conducted in August 2024 to identify potentially relevant studies for use in meta-analysis. This was undertaken because the 2023 draft assessment considered only a single study when determining the evidence base that did not support the derivation of a candidate RfD, and EPA's preference is to conduct meta-analyses for all prioritized health outcomes if possible. Similar to the 2022 update, neurodevelopmental studies identified in the 2024 update underwent risk of bias evaluation and were evaluated against criteria of particular importance for EPA's dose-response meta-analysis.

1.6.2. Evaluation of Individual Studies

The detailed approaches used for the evaluation of epidemiological studies used in the inorganic assessment are provided in the systematic review protocol (link provided in Appendix A, Section 3.9) and summarized in Figure 1-2. Epidemiologic studies containing hazard or dose response data were subject to risk- of- bias (RoB-) evaluations to assess aspects of internal validity of study findings based on study design and conduct for hazard identification. Key concerns are potential bias (factors that affect the magnitude or direction of an effect) and insensitivity (factors that limit the ability of a study to detect a true effect). Risk of bias for each study was evaluated across seven evaluation domains (i.e., selection, confounding, performance, attrition, detection, selective reporting bias, and other) using a tool adapted from the OHAT approach (NTP, 2013)[6] with arsenic-specific clarifications as needed (see below and in Protocol (link provided in Appendix A)). Consistent with a consideration of the strengths and limitations in each domain, risk of bias was assessed for each study question using a rating system with four categories as follows:

[5]In brief, to be included for dose response, a study needed to meet certain key study characteristics (e.g., represent an outcome selected for dose-response, present drinking water, urinary, or toenail levels of arsenic, be a case-control or cohort design, and consider smoking as a confounder), present quantitative information on exposure and outcomes, present quantitative, categorical estimates of exposure, report present the number of cases and control, or person-years), and have other characteristics suitable for inclusion (e.g., be conducted in area considered applicable to U.S. exposure levels, be an incidence study (where necessary), and not be duplicative of other study populations).

[6]The OHAT method was used for this assessment because the current approach being used in IRIS had not been fully developed at the time these study evaluations were being conducted (2012 to 2017).

definitely low bias, probably low bias, probably high bias, and definitely high bias (see the iAs Protocol (link provided in Appendix A), Table 3-3). Evaluations were documented using ICF's DRAGON and Litstream and can now be found in Health Assessment Workspace Collaborative (HAWC). An overall study determination (see below) was based on these individual domain level judgments. Some of the key arsenic-specific evaluation considerations are described here.

Temporality

Temporality between the measurement of exposure and development of the outcome of interest is an important issue in epidemiologic studies. In general, cohort studies are subject to fewer concerns about temporality than other observational study designs due to their prospective nature. However, concerns for lack of temporality in other study designs such as cross-sectional, case-control, and ecological studies can be ameliorated by considering the likelihood that the concurrent exposure measurement is a reasonable proxy of a relevant etiologic period. For example, many of the available cross-sectional studies included populations that had been highly exposed to arsenic at a stable level for more than 5–10 years, which provides increased confidence regarding the suitability of concurrent measures compared with typical cross-sectional study scenarios. In addition, concurrent measurement of exposure is more appropriate for outcomes without a long latency period and analyses where reverse causation is not a concern (i.e., it is unlikely that development of the outcome would influence the measured exposure, or exposure was measured in water).

Ecological Studies: Unique Considerations in the Context of Arsenic

In addition to the temporality concerns discussed above, ecological studies are limited by their lack of individual-level data. In this study design, there is no access to individual-level data and the analyses produce group-level exposure-response functions. However, in the case of arsenic specifically, ecological studies can provide important information to inform causal inference due to well-defined exposure periods, limited population migration, large sample sizes, and large amount of data available helping to reduce the effects of confounding variables. Because of these unusual strengths, several ecological studies were included in the evidence synthesis. The arsenic database also includes ecological studies that function as "natural experiments." These unique exposure scenarios, which include large exposure contrasts, are defined by a clearly identified intervention, provide a natural experiment for evaluation of health hazards. One such example is seen in southwest Taiwan where exposure through drinking water was high—500-fold higher than average drinking water concentrations in the U.S.—but that exposure ceased after drinking water interventions were implemented. Observed associations from natural experiment-ecological studies, particularly in combination with other studies using individual-level data, provide elevated confidence in the observed associations.

Exposure Assessment

The arsenic evidence base contains studies that utilize a variety of approaches, each with their own strengths and weaknesses. In many of these studies, individual exposure was estimated based on arsenic concentrations in drinking water without information on individual-level water intake. This approach is limited by potential nondifferential misclassification for the individual, which is expected to produce bias towards the null (i.e., attenuated effect estimates) on average. Other studies utilized biomarker measures of arsenic, such as in urine, toenail, hair, or blood. An important strength of biomarker studies is that they can better reflect the internal As dose and account for multiple potential sources/routes of exposure. However, there are some concerns with biomarker use as well. For example, the use of total urinary maternal arsenic levels (sum of iAs and urinary arsenic metabolites) to estimate exposure in some studies makes interpreting the exact contribution of iAs difficult when arsenic speciation information is not available during exposure assessment. In humans, inorganic arsenic and methylated metabolites (in urine range from 10%–30% inorganic arsenic, 10%–20% monomethylarsonic acid (MMA) and 60%–80% dimethylarsinic acid (DMA)) are considerably more toxic than organic forms of arsenic (Vahter and Concha, 2001). Organic arsenic is found in fish and shellfish, primarily in the forms of arsenobetaine, arsenosugars, and arsenolipids. As urinary excretion is the main route of elimination for both inorganic and organic arsenic species, in populations with high consumption of seafood, total urinary arsenic could primarily reflect organic arsenical exposure. In this case, the biomarker would not reflect toxic inorganic species well (Martinez-Morata et al., 2023). In order to distinguish between inorganic and organic arsenicals when seafood intake is prevalent in a study population, arsenic speciation and adjustment for arsenobetaine is recommended. Otherwise, the use of total As a biomarker in a population with higher seafood consumption could result in exposure misclassification, which could produce bias to the null, compared with use in a population with lower seafood intake. In other words, in populations with higher seafood intake, total As biomarker measures may provide a less accurate estimate of inorganic As exposure and would likely result in an underestimation of the true effect. For this reason, lack of consideration of speciation (i.e., analytically, statistical analyses) was considered during study evaluation in the exposure characterization domain, especially in populations where seafood consumption could be considered high. However, lack of speciation was not on its own considered a critical deficiency that would preclude consideration of the study for hazard characterization (when applicable) or dose-response analysis. The extent to which arsenobetaine was considered in urine biomarker studies used in dose response is presented in Sections 4.3.1, 4.4, and 4.5, where applicable. There are additional considerations for the use of biomarkers to evaluate exposure during pregnancy (Ashley-Martin et al., 2022).

While hair and nail biomarkers may give an indication of past exposure due to their slow growth, there may also be potential concerns with external contamination (NRC, 1999), although

this concern may be less of an issue for nail biomarker studies compared with hair (Karagas et al., 2001b).

With all methods to assess exposure, there may be nondifferential misclassification if a cohort study utilized only a baseline measure of exposure, but actual exposure is expected to change over time. For example, the half-life of arsenic in urine is approximately 4 days (NRC, 1999), while the half-life in blood is only a few hours (NRC, 1999; Cohen et al., 2006). However, with continuing exposure, as is the case for many populations evaluated in studies considered for this assessment, arsenic biomarkers can represent steady-state and can serve as markers of past exposure. Similarly, even though many studies in the database did not report the gestational age at which arsenic exposure occurred, it was assumed that exposure occurred throughout gestation given the stability of the populations under study.

Urinary Concentration Correction Methods

Spot urine samples used to assess arsenic exposure are typically corrected for urine dilution due to the variable hydration status of study participants. Urine-creatinine and urine-specific gravity are common approaches to correct for physiological variation in water content of urine samples (Hsieh et al., 2019). Comparatively, uncorrected approaches without using timed urine specimens are more prone to introducing exposure measurement bias and therefore hinder accurate exposure assessment.

Data indicate that urinary arsenic corrected by urinary creatinine can be more closely correlated with blood arsenic and water arsenic, compared with urinary arsenic corrected by specific gravity (Abuawad et al.). Yet results from both correction approaches can be similar, compared with uncorrected measures. For example, Kuo et al. (2022) studied the association of arsenic exposure with all-cause, cardiovascular, and cancer mortality evaluated different urinary concentration correction methods, including urine-creatinine and specific gravity, as well as no correction. Similar statistical inferences between urine-creatinine and specific gravity corrections were observed for all-cause and cancer mortality in this adult population (Kuo et al., 2022).

All urinary correction methods have limitations, and it is not possible to pick a clear "best" approach for all scenarios. Urine-creatinine levels can be influenced by factors including age, sex, muscle mass, body mass index, and comorbidities such as diabetes (Barr et al., 2005). Similarly, specific-gravity adjustment has limitations in individuals with kidney damage, metabolic conditions (including diabetes), or cardiovascular disease (Maull et al., 2012; Kuo et al., 2022). This led Kuo et al. (2022) to conclude that, for cardiovascular mortality or metabolic outcomes, the use of specific gravity to correct for urine dilution could result in "… misclassification, overadjustment, or multicollinearity." Ultimately, Kuo et al. (2022) concluded that "… urine-creatinine correction may be a better method to correct for urine dilution when evaluating the effect of arsenic exposure for cardiovascular or metabolic outcomes …" and this conclusion was consistent with the results of the Hsieh et al. (2019) review. Overall, when outcomes under study are also potentially impacted by

factors related to urine-creatinine or specific gravity, judgment is required to select the most appropriate adjustment approach for a given outcome.

In this assessment, lack of urinary correction (either urinary creatinine or specific gravity) was considered during study evaluation in the exposure characterization domain. However, lack of urinary correction was not on its own considered a limitation that would preclude consideration of the study for hazard characterization (when applicable) or dose-response analysis. Yet, for the final dose-response analyses, all studies incorporated an approach to correct for urinary dilution. Creatinine adjustment was most common.

If two approaches were available for urinary correction, expert judgment was used to select the approach carried forward. However, as described below in Section 4, there were scenarios where the outcome-specific dose-response methods dictated the preference for a specific type of urinary correction adjustment approach. More specifically, the El-Masri-Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018a, b) established an empirical relationship between drinking water exposure and creatinine-adjusted urinary total As concentrations (Section 4.1). As such, only studies that reported creatinine-adjusted urinary concentrations were suitable for dose conversion and inclusion in the Bayesian dose-response meta-analysis, which relied on EPA's physiologically based pharmacokinetic model. Specific gravity could be used when creatinine adjustment was not available for outcomes that did not rely on the El-Masri-Kenyon PBPK model for dose conversion.

Impact of Other Factors

Study evaluations for the arsenic assessment incorporated outcome-specific considerations for confounding, as is standard for IRIS assessments. Potential core outcome-specific confounders considered for each of the outcomes are listed below.

- Diseases of the Circulatory System: smoking, sex, age, hypertension, cholesterol, obesity, BMI, measure of SES (e.g., education/income)
- Diabetes: smoking, sex, age, BMI/waist circumference, current use of hypertension medications, smoking, physical activity, measure of SES (e.g., education/income)
- Fetal, newborn, & infant health: maternal smoking/alcohol use, maternal age, race/ethnicity, measure of SES (e.g., education/income), infant sex, parity, gestational age at birth, maternal BMI
- Neurodevelopment: maternal smoking, sex, age, measure of SES (e.g., education/income), birth weight, maternal smoking

With regard to consideration of seafood intake, approaches varied: some studies adjusted for seafood consumption, such as through speciating urinary arsenic and excluding arsenobetaine. Others confirmed low seafood consumption in the study population or asked participants not to consume seafood prior to study inclusion. Other studies did not address potential confounding by

organic arsenic by seafood intake. Lack of consideration of speciation (in design or analysis) was considered during study evaluation, especially in populations where seafood consumption could be considered high. However, lack of speciation was not on its own considered a limitation that would preclude consideration of the study for hazard characterization (when applicable) or dose-response analysis.

Several outcomes impacted by arsenic exposure may be interrelated through mediation or confounding. For example, hypertension and diabetes could potentially be on the causal pathway between arsenic exposure and IHD; alternatively, they could confound the association. Similarly, low birth weight could potentially be on the causal pathway between arsenic and neurodevelopment, or alternatively confound the association. If a study appropriately adjusts for a confounder, potential bias from that confounder would be removed in the calculated effect estimate. If a study adjusts for a variable on the causal pathway (i.e., a mediator), the calculated effect estimate would not include any effect from the mediating variable. A model that included potential mediators would not have been preferred for analysis. Yet, converging findings of the adverse impacts of arsenic using varying approaches to adjustment provide more confidence in the overall conclusions and indicate a logical coherence in the evidence base. However, not all studies collected or accounted for information on interrelated outcomes consistently in their analyses. As such, expert judgment was an important aspect of the study evaluation process to determine the impact of varying approaches on the overall risk of bias.

Overall Study Confidence Determination

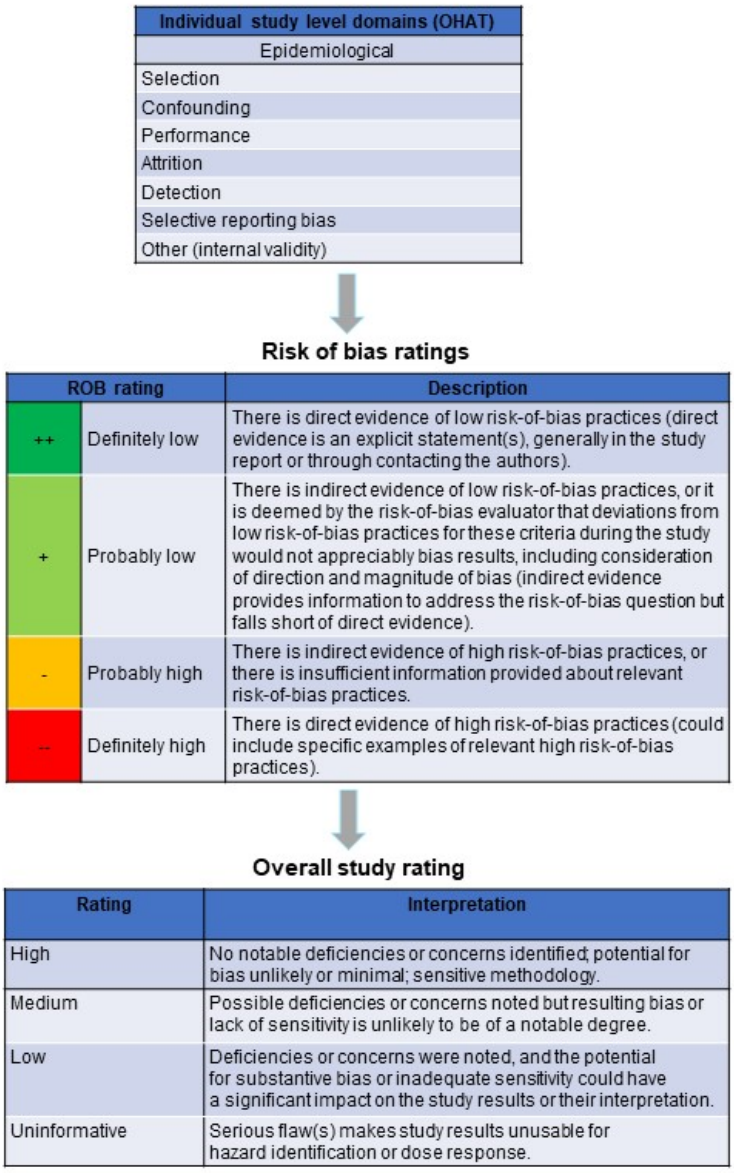
Once all evaluation domains were evaluated, the identified strengths and limitations were collectively considered by the reviewers to reach a final study confidence classification. Study evaluations are holistic judgments based on all domains considered. A judgment of deficient (or the equivalent in the prior system for study confidence) in one domain does not necessarily mean that the entire study is *low* confidence or unsuitable for dose-response. The study evaluations are aimed at discerning limitations that could substantively change a result presented in the study or the interpretation of that result, also considering the expected direction of the bias. There are no defined weights for the domains, and study reviewers are responsible for applying expert judgment to make the determination of overall study confidence rating. Recognizing the role of expert judgment in the process, evaluations are conducted at the health outcome level by at least two reviewers with documentation of the supporting rationale for each rating. After independently reviewing a study, the two reviewers discussed differences and resolved any discrepancies between their ratings and rationales. Conflict resolution by an additional reviewer was done as needed. Thus, the reviewers reached a consensus judgment regarding each evaluation domain and overall (confidence) determination. The study evaluation results were carried forward to inform evidence synthesis analyses. Overall study confidence determinations are defined below:

- *High* confidence: No notable deficiencies or concerns were identified; the potential for bias is unlikely or minimal, and the study used sensitive methodology.

- *Medium* confidence: Possible deficiencies or concerns were noted, but the limitations are unlikely to be of a notable degree or to have a notable impact on the results.

- *Low* confidence: Deficiencies or concerns were noted, and the potential for bias or inadequate sensitivity could have a significant impact on the study results or their interpretation. *Low* confidence results were given less weight than *high* or *medium* confidence results during evidence synthesis and judgment.

- *Uninformative*: Serious flaw(s) were identified that make the study results unusable. *Uninformative* studies were not considered further, except to highlight possible research gaps.



Individual study level domains (OHAT)
Epidemiological
Selection
Confounding
Performance
Attrition
Detection
Selective reporting bias
Other (internal validity)

Risk of bias ratings

ROB rating		Description
++	Definitely low	There is direct evidence of low risk-of-bias practices (direct evidence is an explicit statement(s), generally in the study report or through contacting the authors).
+	Probably low	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	There is indirect evidence of high risk-of-bias practices, or there is insufficient information provided about relevant risk-of-bias practices.
--	Definitely high	There is direct evidence of high risk-of-bias practices (could include specific examples of relevant high risk-of-bias practices).

Overall study rating

Rating	Interpretation
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal; sensitive methodology.
Medium	Possible deficiencies or concerns noted but resulting bias or lack of sensitivity is unlikely to be of a notable degree.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results unusable for hazard identification or dose response.

Figure 1-2. Study evaluation overview of epidemiological studies.

1.6.3. Data Extraction and Visualizations

The detailed data extraction approach is provided in the iAs Protocol (link provided in Appendix A), Section 3.11. Data extraction and content management was initially carried out using ICF's DRAGON and Litstream before subsequent migration to HAWC in 2021. Not all studies that meet the PECO criteria went through data extraction. Given the abundance of studies*, medium* or *high* confidence studies were prioritized over *low* or *uninformative* studies for extraction and presentation in the assessment. Studies evaluated as *uninformative* were not considered further and therefore did not undergo data extraction and were not cited in the assessment. *Low* confidence studies did undergo extraction but were not incorporated into evidence synthesis

analysis or forest plots due to the availability of a large number of *medium* and *high* confidence studies. Literature tag-trees contain lists of all studies tagged as *uninformative*, *low* confidence, *medium* confidence, and *high* confidence for each outcome (see Figures 3-3, 3-22, 3-27, 3-39).

All findings from *medium* or *high* confidence studies were considered for extraction, regardless of the statistical significance of their findings. Only results from the model that considered the most outcome-specific confounders (see Section 1.6.2 for core confounders) were selected for extraction. This was often the most fully adjusted model, but not always. For example, a model that included potential mediators would not have been preferred for data extraction and display (see Section 1.6.2 "Impact of Other Factors"). For quality control, data extraction was performed by one member of the evaluation team and independently verified by at least one other member. Discrepancies in data extraction were resolved by discussion or consultation within the evaluation team. Results from all *medium* and *high* confidence studies are visualized in figures throughout Section 3.2.

To be included in a forest plot, study results had to meet the following criteria (study results that did not fit criteria were listed or further described in Section 3.2 narrative):

- Must include a ratio measure or difference measure.
- At least two estimates that were generally comparable were required in order to create a plot. A forest plot was not created if the plot would only display a single estimate. For example, there was a single effect estimate for the grouping: *Diseases of the Circulatory System, Ischemic Heart Disease, Ecological study design*, therefore Tsai et al. (1999) does not appear in a plot.

Studies were grouped in the following order for presentation in forest plots:

- Outcome (DCS, Diabetes, Fetal and Infant Health. Neurodevelopment)
- Sub-outcome (if relevant)
- Study design (DCS, diabetes, and developmental neurocognitive sections only, given the large number of studies to display)
- Effect estimate (Ratio or difference measures)
- Exposure assessment (Biomarker or drinking water)
- Estimate of exposure (Categorical or continuous)

In the forest plots, the country where each epidemiology study was conducted was presented to provide information on relative environmental exposure levels. For summary purposes, higher exposures were considered to be from countries such as Bangladesh, China, and Chile, while lower exposures include the United States, Mexico, and Denmark. The intent of the figures is to facilitate qualitative analyses of patterns of associations across studies. Figures include

studies that vary across different dimensions, such as the use different types of effect estimates, different exposure assessment techniques as described in the column labeled "Exposure metric," the use of different reference and exposure groups, different transformations of the exposure variable, and different increments of arsenic for associated regression coefficients. Thus, quantitative comparisons of the magnitude of the associations between studies is not appropriate. In addition, comparisons between plots may not be appropriate as both logarithmic and arithmetic scales are used. Targeted supplemental data pivots for scenarios with maximum arsenic exposures ≤100 μg/L in drinking water were developed based on the following criteria: for studies based on drinking water exposure, analyses were included if the categorical exposure category was ≤100 μg/L or if the maximum concentration in the study population was ≤100 μg/L for continuous exposure. For studies based on biomarker of exposure, analyses were included if the authors documented or referenced secondary information indicating that the maximum arsenic concentration in drinking water for the study population was ≤100 μg/L.

1.6.4. Evidence Synthesis of Epidemiological Evidence

EPA has recognized arsenic as a known human carcinogen since 1988 (U.S. EPA, 1993, 1995). Skin, bladder, and lung cancer and skin lesions are acknowledged as known hazard outcomes for inorganic arsenic (NRC, 2013; IARC, 2004b, 2012; Health Canada, 2006; ATSDR, 2007) and were considered in the updated problem formulation and protocol (link provided in Appendix A) to have a human evidence synthesis judgment of *robust*. This assessment develops new evidence synthesis conclusions for diseases of the circulatory system, fetal, newborn, and infant health outcomes, neurodevelopmental effects, and diabetes. Although skin cancer and skin lesions are acknowledged as known hazard outcomes they were not considered for dose-response analyses in this assessment based on an initial relative risk over background screening analyses [see Section 5.1 of the protocol, link provided in Appendix A and Hobbie et al. (Hobbie et al., 2020)]. In brief, skin cancer and skin lesions did not seem likely to drive cancer dose-response conclusions, i.e., skin cancer and skin lesions had margin of exposure values at relatively high exposures not generally encountered in the U.S. In addition, the vast majority of studies on these outcomes did not meet the screening criteria for inclusion for dose-response (see iAs Protocol, Section 5 (link provided in Appendix A)) and of those that did (one study for skin lesions, two studies for skin cancer [basal cell carcinoma or squamous cell carcinoma]), none were expected to be drivers of dose-response conclusions in the assessment.

Each synthesis is written to provide a summary discussion of the available evidence that addresses considerations that may suggest causation adapted from considerations for causality using a structured evaluation of an adapted set of considerations first introduced by Sir Bradford Hill (Hill, 1965) including consistency, exposure-response relationship, strength of the association, temporal relationship, coherence, and "natural experiments" in humans (U.S. EPA, 1994, 2005a) (see the iAs Protocol (link provided in Appendix A), Table 3-5). Importantly, the approach to the

process of evidence synthesis explicitly considers and incorporates the conclusions from the individual study evaluations.

Evidence synthesis was based on epidemiology studies of *high* and *medium* confidence given the size of the iAs evidence base. Syntheses articulated the strengths and the weaknesses of the available evidence organized around the considerations described in the iAs Protocol (link provided in Appendix A), Table 3-5 as well as issues that stem from the evaluation of individual studies (e.g., concerns about bias or sensitivity). The analysis typically included examination of results stratified by any or all of the following: study confidence classification (or specific issues within confidence evaluation domains), population, exposures (e.g., level, patterns [intermittent or continuous], duration, intensity), sensitivity (e.g., low vs. high), and other factors that were identified in the refined evaluation plan (e.g., sex, life stage, or other demographics). Study sensitivity assesses whether factors in the study's design and conduct may reduce its ability to observe an effect if present. The number of studies and the differences encompassed by the studies determined the extent to which specific types of factors can be examined to stratify study results.

The analyses of several considerations (see the iAs Protocol (link provided in Appendix A), Table 3-7) were used to develop a strength-of-evidence judgment. The terms associated with the different strength of evidence judgments for the epidemiological evidence on each of the assessed health outcomes are *robust*, *moderate*, *slight*, *indeterminate*, and *compelling evidence of no effect*. The final output is a summary judgment of the evidence base for each potential human health effect based on epidemiological evidence. The terms associated with these summary judgments are *evidence demonstrates*, *evidence indicates (likely)*, *evidence suggests*, *evidence inadequate*, and *strong evidence of no effect*. These judgments were reached utilizing considerations based on the human evidence given the scope of the assessment [(U.S. EPA, 2022) Handbook Table 11-5]. *Robust* evidence from humans leads to the strongest evidence integration conclusion of *evidence demonstrates* (U.S. EPA, 2022). For evaluations of carcinogenicity consistent with EPA's Cancer Guidelines (U.S. EPA, 2005a), one of EPA's standardized cancer descriptors was used as a shorthand characterization of the evidence integration narrative, describing the overall potential for carcinogenicity. These are (1) *carcinogenic to humans*, (2) *likely to be carcinogenic to humans*, (3) *suggestive evidence of carcinogenic potential*, (4) *inadequate information to assess carcinogenic potential*, or (5) *not likely to be carcinogenic to humans*. Because bladder cancer and lung cancer are accepted hazards, the corresponding cancer descriptors for these health outcomes are carcinogenic to humans.

1.6.5. Dose-Response Analysis

The dose-response methods employed in this assessment are summarized in Appendix C and detailed in several publications (Mendez et al., 2020; Hobbie et al., 2020; Allen et al., 2020b; Allen et al., 2020a). The dose-response methods adhere to existing EPA guidelines and support documents, especially EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), EPA's *Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b), *Guidelines for*

Carcinogen Risk Assessment (U.S. EPA, 2005a), and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), and evolving practices in the IRIS program in consideration of recommendations provided by the National Academies of Sciences, Engineering, and Medicine and the National Research Council (NRC, 2001, 2009, 2011, 2013, 2014; NASEM, 2019, 2021).

As recommended by the NRC (2013) and supported during the 2019 NASEM review of the protocol (NASEM, 2019), EPA focused its dose-response analysis on epidemiological data. Given the extensive epidemiological evidence base of iAs studies, a screening level of modeling was performed to help prioritize endpoints and studies for dose-response analysis (Hobbie et al., 2020). The primary objectives of the exposure-response screening were to help identify health outcomes that warrant and allow for multiple-study dose-response meta-analyses, select the most appropriate data sets for modeling, and provide screening-level relative risk estimates for a broad set of health outcomes potentially useful for cost-benefit considerations. The screening analysis involved deriving and comparing study/data set-specific unitless ratios of the exposure associated with a defined relative risk increase over the background exposure (RRB) (Hobbie et al., 2020).

On the basis of the screening analysis results, more complex Bayesian dose-response meta-analysis dose-response analyses (Allen et al., 2020b; Allen et al., 2020a) were performed using select epidemiological studies for bladder cancer, lung cancer, diseases of the circulatory system (DCS) and diabetes (see Section 5.1 of the Protocol).[7] In brief, for study selection, a series of study design considerations were applied to *medium* or *high* confidence studies to identify studies for dose response analysis. To be included, a study needed to meet certain key study characteristics (e.g., represent an outcome selected for dose-response, present drinking water, urinary, or toenail levels of arsenic, be a case-control or cohort design, and consider smoking as a confounder), present quantitative information on exposure and outcomes (e.g., report findings as odds ratio (OR), relative risk (RR), or hazard ratio (HR), present quantitative, categorical estimates of exposure, report present the number of cases and control, or person-years), and have other characteristics suitable for inclusion (e.g., be conducted in area considered applicable to U.S. exposure levels, be an incidence study (where necessary), and not be duplicative of other study populations). A stopping approach was used where the considerations were applied in a sequence and a study did not advance further if an inclusion criterion was not met.

The specific sequence of applying inclusion criteria sometimes varied across outcomes in order to increase efficiency of the process. For example, for lung cancer and bladder cancer the outcomes were already narrowed during hazard identification whereas several noncancer outcomes (diabetes, neurodevelopment, cardiovascular) needed to be further specified for dose-

[7]The decision to not include some endpoints in the more complex Bayesian meta-regression analysis should not be interpreted to mean EPA dismisses these endpoints as health effects of concern with iAs exposure. Rather, the Agency focuses on the selected six endpoints as these were prioritized to better represent the toxicological profile for iAs.

response analysis. The studies cited in evidence synthesis for diabetes (Section 3.2.2) included type 2 diabetes, type 1 diabetes, gestational diabetes, metabolic syndrome, and insulin resistance. However, dose-response focused on type 2 diabetes so confirming type 2 diabetes as the outcome was an early consideration in the stopping sequence. For neurodevelopmental effects and fetal, newborn, and infant health outcomes, confirming that studies investigated cognitive effects or birthweight (respectively) was an early consideration in the stopping sequence for study selection. For diseases of the circulatory system, the focus for dose-response was ischemic heart disease so confirming a study investigated ischemic heart disease (or atherosclerosis) was added to end of study selection workflow for diseases of the circulatory system. The specific study selection sequence applied to each health outcome is presented when displaying the results of this screening process in Sections 4.3, 4.4, and 4.5.

Additionally, fetal, newborn, and infant health outcomes and developmental neurotoxicity (i.e., developmental neurocognitive effects) were identified as being particularly important to EPA Program Offices for cost-benefit analyses and were thus prioritized for inclusion in the assessment. While the datasets for fetal, newborn, and infant health outcomes and neurodevelopmental, neurocognitive effects were not amenable to the Bayesian dose-response meta-analysis approach, they contained dose-response data that could be evaluated by other methods.

The dose-response meta-analysis approach used in this assessment involves the application of a flexible, nonlinear, logistic-power model to derive U.S. population-specific mean extra risk estimates with confidence intervals that reflect the uncertainty in the logistic-power slope estimates. Linear (cancer endpoints only) approximations (for estimating CSFs) and polynomial equations are fit to these risk-at-a-dose values. The linear relationships between the upper-bound risk and dose presented in this assessment are analogous to cancer slope factor (CSF) estimates that EPA has historically provided for cancer risks. The CSF approximate the upper-bound lifetime extra cancer risk from chronic ingestion of a chemical per unit of mass consumed per unit body weight per day (expressed as $[\mu g/kg\text{-}day]^{-1}$). To calculate the exact mean or upper-bound lifetime extra risk at any dose, the lifetable approach can be applied using the dose of interest. EPA has provided endpoint-specific lifetables as supplemental materials so that these calculations can be performed.

The approaches EPA used to identify and address susceptible populations and lifestages and to quantify uncertainty and variability are summarized in Section 5.2 of the Protocol (link provided in Appendix A). In part, this involved the use of flexible dose-response models, model averaging, and Bayesian dose-response meta-analysis and sensitivity analyses to determine the impact of priors and other modeling assumptions. Sections 4.2 through 4.6 provide details concerning the application of these approaches to individual health outcomes and relevant endpoints.

Most of the epidemiological evidence for the bladder cancer, lung cancer, diabetes and DCS health outcomes is from general population cohort and case-control studies that report the relationship between increasing iAs exposure groups and relative risks (RRs) above a reference

group (RR = 1). The reference group exposure differs for each study included in the dose-response meta-analysis. In this assessment, EPA's dose-response meta-analyses estimate a health outcome-specific average (logistic-power model) slope and power parameter for that relationship across studies, then uses it to predict mean and upper-bound lifetime extra risks above an estimate of the U.S. risk at a zero iAs dose. An estimate of the zero-dose risk is obtained by extrapolation, using the logistic slope estimates obtained from the dose-response meta-analysis and assuming that U.S. lifetime background risks are associated with EPA's U.S. background dose estimate of 0.0365 μg iAs/kg-day,[8] 0.02 μg iAs/kg-day from dietary food consumption (Xue et al., 2010) and 0.0165 μg iAs/kg-day from drinking water.[9] Where possible, U.S. background risks are estimated using published lifetables. An important aspect of the lifetable applications is that the exposure scenario used posits a continuous, full lifetime exposure to a constant iAs dose (see Section 4.3.4 for details).

This assessment derives separate oral noncancer reference doses (RfDs) for several endpoints, including IHD (defined as incident or fatal cases), diabetes, fetal, newborn, and infant health outcomes, and developmental neurocognitive effects. A single overall RfD is selected to cover all health outcomes across all organs/systems. Although this overall RfD represents the focus of these dose-response assessments, the organ/system-specific values can be useful for subsequent cumulative risk assessments that consider the combined effect of multiple exposures acting on a common organ/system or mechanism.

[8]EPA's iAs PBPK model indicates that this level of intake is consistent with the estimated 1-5 μg/L urinary background levels of total arsenic (summing inorganic, monomethyl, and dimethyl arsenic forms) that NRC (2013) considered to a reasonable for the U.S. population.

[9]Using median U.S. dietary consumption (Xue et al., 2010) and median U.S. Country average inorganic arsenic drinking water concentration (1.5 μg/L) from USGS data, (Mendez et al., 2017) multiplied by the average water intake rate in the U.S. population of 0.011 L/kg-day (U.S. EPA (2019), Table 3-1, "All Ages").

2. LITERATURE SEARCH AND STUDY EVALUATION RESULTS

2.1. LITERATURE SEARCH AND SCREENING RESULTS

The database searches conducted between January 2013 and January 2019 yielded 35,964 unique studies (see Figure 2-1 and Figure 2-2). Software workflows have evolved since 2013; thus, Figure 2-1 shows the initial literature search and updates through 2015, and Figure 2-2 shows literature searches conducted from October 2015 through January 2019. Of the 35,964 studies identified, 33,337 were excluded during initial filtering and title and abstract screening, 1003 were reviewed at the full-text level. Of the 1003 screened at full-text level, 354 epidemiological studies were considered to meet PECO criteria (see Table 1-2). A literature search update conducted August 2022 yielded an additional 169 PECO relevant studies (see Figure 2-2 and Appendix B.3), and studies with hazard and/or dose-response utility were integrated. An additional literature search update focusing on neurodevelopmental effects, conducted in August 2024, identified 15 PECO relevant studies for consideration in in meta-analysis. Literature search and screening results are summarized in HAWC.

2.2. STUDY EVALUATION RESULTS

The study evaluations of the available epidemiological studies for bladder cancer, lung cancer, DCS, diabetes, fetal, newborn, and infant health outcomes, and neurodevelopmental effects are summarized in HAWC. The evidence synthesis analysis of studies with health outcome judgment of *medium* or *high* confidence are discussed in Section 3.2.

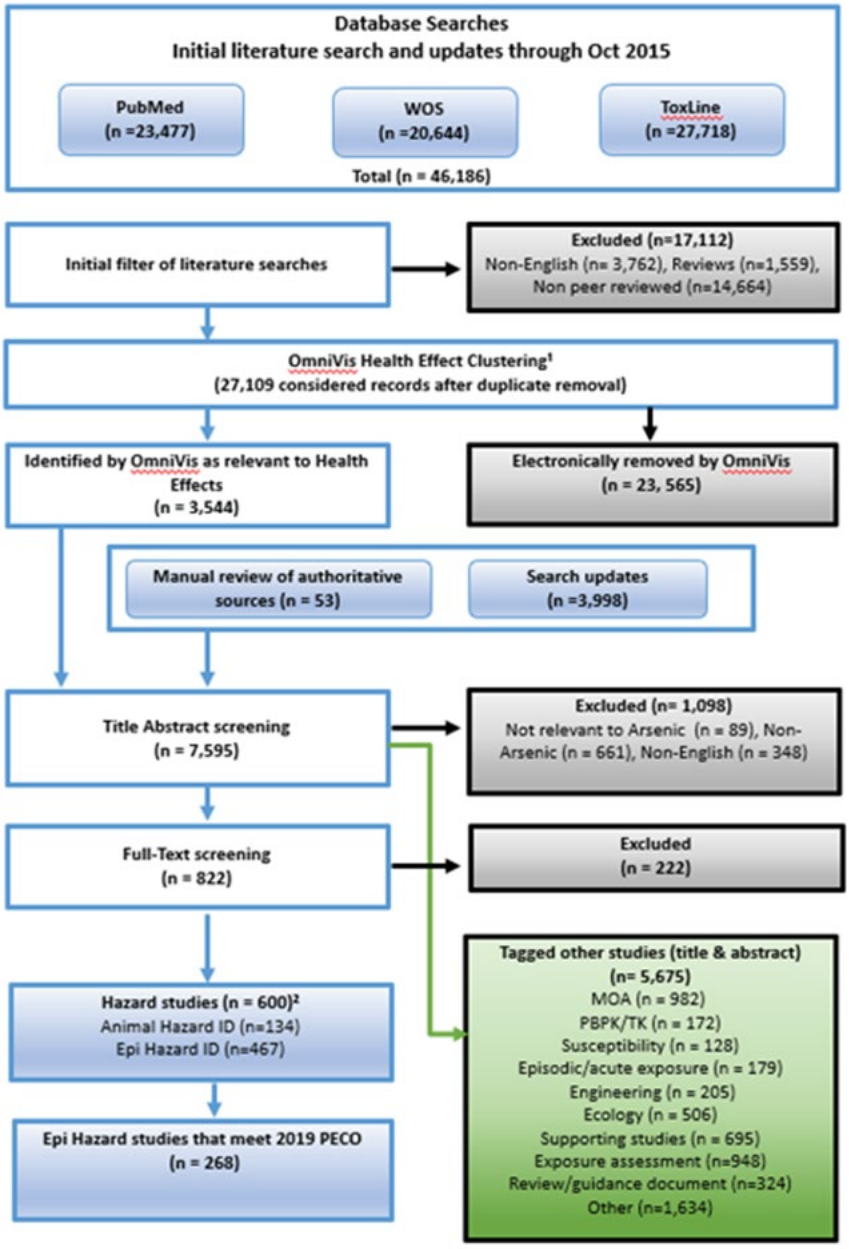


Figure 2-1. Literature search and screening flow diagram for inorganic arsenic (initial database search and updates through 2015).

[1] Initial results only

[2] Studies may be in multiple groups

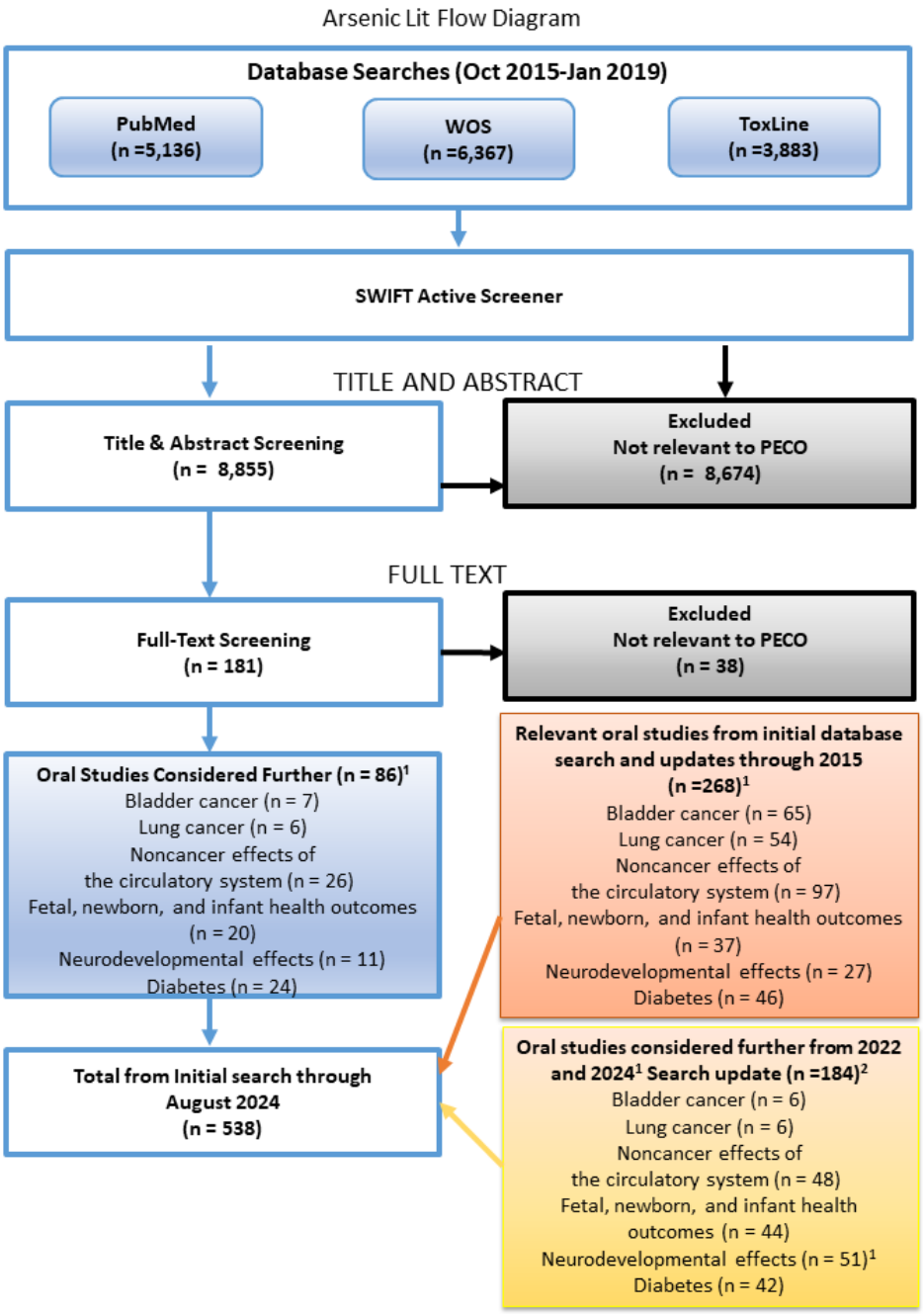


Figure 2-2. Literature search and screening flow diagram for inorganic arsenic (October 2015 to January 2019; 2022 search update; 2024 search update focused on neurodevelopmental effects).

[1]15 neurodevelopmental studies identified in August 2024 search update

[2]Studies may be in multiple groups

3. PHARMACOKINETICS AND EVIDENCE SYNTHESIS

3.1. PHARMACOKINETICS

The behavior of arsenic in the body is complex. After absorption, inorganic arsenic undergoes a complicated series of enzymatic and nonenzymatic oxidation, reduction, and conjugation reactions. Although all these reactions can occur throughout the body, the rate at which they occur varies greatly from organ to organ. In addition, there are important differences in arsenic metabolism across animal species (Drobná et al., 2010), and these variations make it difficult to identify suitable animal models for predicting human metabolic patterns.

Each metabolic transformation affects the subsequent biokinetic behavior (transport, persistence, elimination) and pharmacokinetics of the arsenic species. Thus, absorption, transport, and metabolic processes are highly interdependent and cannot easily be discussed separately. The general pattern involves the gastrointestinal (GI) absorption of inorganic arsenic species, followed by a cascade of oxidation-reduction reactions and methylation steps, resulting in the partial transformation of the inorganic species into mono- or dimethylated species (collectively referred to as MMA and DMA, recognizing that there is often ambiguity in characterizing the oxidation state of the methylarsenic compounds). Conjugated arsenic species, either methylated or not (e.g., glutathione conjugates or other sulfur-containing derivatives), also may be produced.

Several metabolic schemes have been proposed that describe the general pathway that converts inorganic arsenic to its primary metabolites MMA and DMA, regardless of exposure route. These pathways involve numerous enzymes and cofactors. Some of the proposed metabolic pathways involve the cycling of arsenic species back and forth between the +3 (trivalent) and +5 (pentavalent) oxidation states, and there is evidence that key metabolic processes may be saturable, so that metabolic patterns differ with exposure levels. MMA, DMA, and inorganic arsenic levels in tissues, blood, and urine are the most frequently measured metabolites; the relative levels of these compounds in blood or urine are often the primary evidence in support of one or another metabolic pathway. Genomic tools are being increasingly employed to better characterize human arsenic metabolism and to identify individuals at higher risk from arsenic exposures (Wood et al., 2006; Pierce et al., 2012; Engström et al., 2013).

A general metabolic scheme for inorganic arsenic, illustrating the biotransformation in humans, is shown below in Figure 3-1. A more detailed discussion of inorganic arsenic pharmacokinetics is provided in Appendix D.

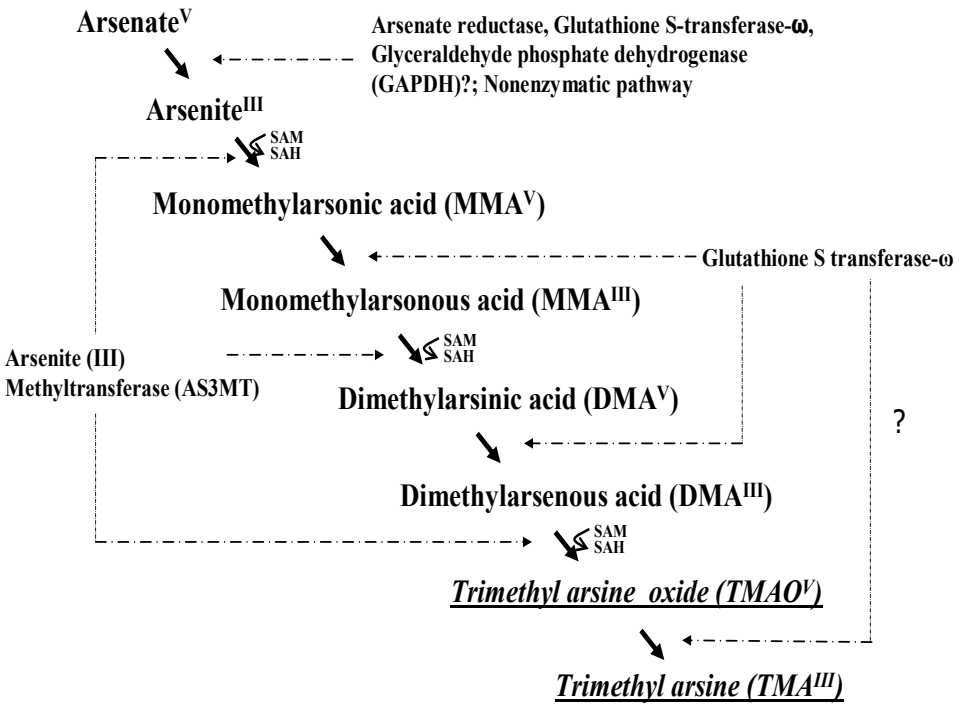


Figure 3-1. Biotransformation of inorganic arsenic in humans.

Source: Sams et al. (2007)

3.1.1. Description of *Pharmacokinetic Models*

Physiologically based pharmacokinetic (PBPK) models for inorganic arsenic are important for describing exposure-internal dose relationships and, thus, informing dose-response estimates. The development of useful biologically-based dose-response models has proved to be challenging because inorganic arsenic can mediate its toxicity through a range of metabolites, and their roles with regard to specific adverse effects are not clear (Clewell et al., 2007). PBPK models have been developed specifically for inorganic arsenic exposure (Mann et al., 1996a; Yu, 1999; Mann et al., 1996b; Gentry et al., 2004; Gentry et al., 2005; Kenyon et al., 2008; El-Masri and Kenyon, 2008; El-Masri et al., 2018a; El-Masri et al., 2018b). These models were evaluated following methods in the ORD's Quality Assurance Project Plan (QAPP) (L-CPAD-0032188-QP-1-2), and the El-Masri-Kenyon model was chosen as the most appropriate (see iAs Protocol, Appendix E [link provided in Appendix A]). In brief, the El-Masri-Kenyon model was selected because it incorporated more complex metabolic mechanisms with parameters that were independently derived from experimental and literature data (Kenyon, 2021).

The El-Masri-Kenyon model was then evaluated using two large data sets (~11,000 and 500 subjects in Bangladesh and Nevada, respectively) which provided matched individual chronic arsenic drinking water exposure and urinary excretion. Quantitative relationships between exposure in drinking water and urine levels of inorganic arsenic were developed for well-studied

populations (Bangladesh, Taiwan, U.S., males and females) using age- and population-specific conversions in the dose estimates. The El-Masri-Kenyon model was considered to adequately predict measured data for the overall oral exposure to inorganic arsenic (El-Masri et al., 2018a; El-Masri et al., 2018b)(see Figure 3-2, Bangladesh data shown).

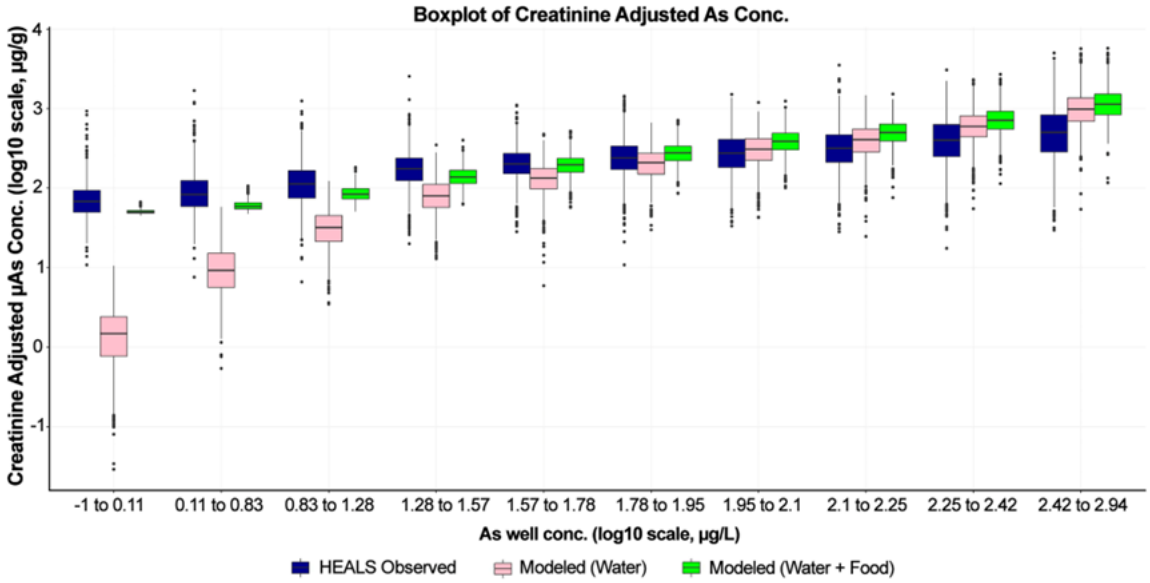


Figure 3-2. El-Masri-Kenyon PBPK model calibration against measured iAs total urinary concentrations and drinking water concentrations.

Ultimately, the El-Masri-Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018a; El-Masri et al., 2018b) establishes an approximate 1:1 empirical relationship between the total urinary arsenic mg/day excretion and the mg/day oral consumption of inorganic arsenic (see Table 3-1 below).

Table 3-1. Relationship between daily iAs dose and daily urinary tAs excretion

Daily iAs dose (mg/d)	Total As urinary excretion rate (mg/d)
0.001	9.5e−4
0.01	0.0095
0.02	0.019
0.04	0.038
0.05	0.048
0.1	0.095
0.15	0.143
0.3	0.29
1	0.95
1.5	1.42
2	1.9
10	9.2
50	45.2

3.2. EVIDENCE SYNTHESIS

This assessment focuses on cancer and noncancer outcomes including bladder cancer, lung cancer, DCS, fetal, newborn, and infant health outcomes, neurodevelopmental effects, and diabetes. The prioritization of these health outcomes was based on prior feedback from (NRC, 2009; NRC, 2013; NRC, 2014; NASEM, 2019) and availability of evidence. Because bladder cancer and lung cancer are accepted hazards of inorganic arsenic exposure (WHO, 2011a; NTP, 2016; Lynch et al., 2017a; IARC, 2004b; ATSDR, 2007; ATSDR, 2016), the strength of evidence for these health outcomes was considered *robust*, and no new evidence synthesis was conducted by EPA. This assessment focuses on studies for these outcomes considered most suitable for dose-response analysis. New evidence synthesis analysis was conducted for DCS; fetal, newborn, and infant health outcomes (i.e., fetal, and infant loss, fetal growth, prematurity, birth weight, and growth in the first 10 years of life); neurodevelopmental effects; and diabetes (see Section 1.6 and the Protocol for Assessment Methods).

Noncancer

3.2.1. Diseases of the Circulatory System

Database Overview

In 2013, the NRC concluded that low-to-moderate (<100 μg/L in drinking water) levels of inorganic arsenic are associated with cardiovascular disease based on evidence from human studies (NRC, 2013). As a result, evaluation of cardiovascular disease was recommended for consideration for dose-response analysis in the IRIS Toxicological Review. On the basis of the analysis of epidemiological evidence, the strength of evidence judgment for a causal association was considered "robust." *Robust* evidence from humans leads to the strongest evidence integration conclusion of **evidence demonstrates** (U.S. EPA, 2022). This section summarizes the review of the available evidence demonstrating a conclusion that exposure to iAs causes diseases of the circulatory system.

There are 169 epidemiological publications that examined the relationship between iAs exposures and diseases of the circulatory system (see Figure 3-3). One hundred and twenty-two of these publications underwent study evaluation; 93 studies (including one study (Nigra et al., 2021) that was identified post-2019 and considered only for dose-response analysis) were considered *medium* or *high* confidence and the remaining 29 were considered *low* or *uninformative*. Forty-seven studies were identified post-2019 and were not considered further for hazard identification or dose-response (see Section 1.6.1). The study evaluations for all the epidemiologic studies are summarized in HAWC. Given the abundance of studies, the synthesis below focuses on conclusions from the *high* and *medium* confidence studies. Citations of studies broken down by confidence level, type of cardiovascular outcome, and studies identified in the 2022 update can be accessed via the interactive HAWC literature tag-tree visual presented in Figure 3-3.

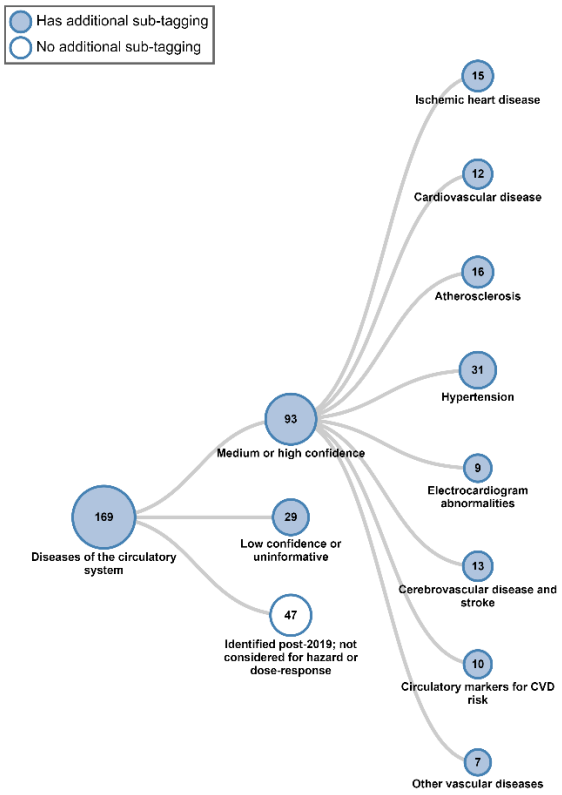


Figure 3-3. Literature tree of epidemiological studies assessing diseases of the circulatory system (see interactive version in HAWC).

In many of these studies, individual exposure was measured by using arsenic concentrations in drinking water to measure chronic and/or current exposure. The populations examined in the epidemiological studies were exposed to mean concentrations of iAs in drinking water over their lifetimes (or specified durations) ranging from <10 µg/L to approximately 930 µg/L. Other studies utilized biomarker measures of arsenic, such as in urine, toenail, hair, or blood. Strengths and weaknesses of biomarker and drinking water exposure assessment approaches are discussed in Section 1.6.2. The most informative studies for both water and biomarker exposure measures are those that included a range of concentrations and had adequate sample size across that range.

Studies conducted in southwest Taiwan are discussed separately within subsections, when available, due to their limited relevance to U.S. populations, where the average drinking water concentrations are 500-fold lower, and the highest concentrations observed are still 10- to 100-fold lower. Additionally, many of these studies are unique "natural experiments," examining pre- and post-intervention arsenic exposures. For more background on this population see Section 1.6.2. Mechanistic observations are also summarized in this section.

Finally, this section discusses how an association between iAs, and CVD outcomes might be influenced by potential risk modifiers (e.g., environmental co-exposures, life stage, sex).

Evidence from Epidemiological Studies

For the purpose of defining the scope of this section, diseases of the circulatory system (DCS) [10] include cardiovascular diseases (CVDs) such as ischemic heart disease (IHD) (known as coronary heart disease [11]), hypertension, cerebrovascular disease and stroke, and peripheral vascular diseases (PVDs). Studies describing inorganic arsenic exposure and related intermediate endpoints and/or risk factors for DCS are also considered.

Cardiovascular disease (CVD) is an umbrella term, referring to diseases of the heart and blood vessels. Among the most common CVD that is studied in relation to inorganic arsenic exposure is IHD, also called coronary heart disease. Typically, IHD refers to heart conditions caused by narrowed coronary arteries that supply blood to the heart muscle. When blood flow is completely blocked, tissue death in the heart occurs, which is known as a heart attack or myocardial infarction (MI). The literature base includes intermediate endpoints that are evaluated when making a CVD or IHD diagnosis, such as hypertension, atherosclerosis, and electrocardiogram abnormalities. The arsenic literature includes studies of exposure to inorganic arsenic and its association with hypertension, i.e., persistently elevated blood pressure, and/or subclinical changes in blood pressure metrics (e.g., systolic blood pressure, diastolic blood pressure, and pulse pressure). Hypertension is both a risk factor for CVD, IHD, and stroke, and is a heart disease that promotes left ventricular hypertrophy (LVH) and heart failure. QT prolongation, which is a repolarization abnormality that is associated with an overactivity in the sympathetic tone (Solti et al., 1989), frequently presents with LVH and is associated with an increased risk of sudden death. Stress induced increases in blood pressure are also consistent with sympathetic hyperreactivity and may indicate a potential trigger for hypertension.

The atherogenic effect of inorganic arsenic exposure can be studied by measuring carotid intima-media thickness (cIMT) using ultrasonography. It can also be studied by examining its relationship with biomarkers that indicate vascular inflammation or endothelial dysfunction (e.g., soluble intercellular adhesion molecule-1 [sICAM-1] and soluble vascular adhesion molecule-1 [sVCAM-1], plasma asymmetric dimethylarginine [ADMA]) and the interaction between inorganic arsenic exposure and genetic variants related to endothelial dysfunction. Cerebrovascular diseases such as ischemic stroke, which may result from an obstruction within a blood vessel that supplies oxygen to the brain, are also studied in relation to arsenic exposure.

Lastly, the literature on the health effects of endemic arsenic exposure in southwest Taiwan where the population was exposed to high arsenic concentrations (mean concentrations ranging from 700–930 μg/L) over decades, includes studies of Blackfoot disease, which is a PVD that is characterized by progressive arterial occlusion in the lower extremities and gangrene (Pan et al.,

[10]This terminology is consistent with the latest International Classification of Disease-10 (https://icd.who.int/browse10/2016/en#/).
[11]CHD is largely synonymous with IHD but has no specific ICD code; studies that use the term CHD to define cases are included in the IHD sections of this assessment.

1993; Chen et al., 1988). Because of the potential for arsenic to affect the peripheral vascular system, epidemiologic studies of Raynaud's phenomenon, and subclinical indicators of PVD as defined by ankle-brachial index and response to cold stress, have been conducted in a variety of populations.

Ischemic Heart Disease

The literature review identified 15 epidemiological studies that were considered medium or high confidence that evaluated the association between iAs exposure and ischemic heart disease (IHD). Fourteen of those studies are reviewed in this section. (One study (Nigra et al., 2021) was identified post-2019 and considered only for dose-response analysis.) Studies used different methods to determine IHD mortality or incidence; this included ICD codes, medical chart review by expert committee, electrocardiography (ECG) results and history of myocardial infarction, and death certificates adjudicated by an expert panel. All eligible studies that reported effect estimates (see Section 1.6.3) are summarized in Figure 3-4.

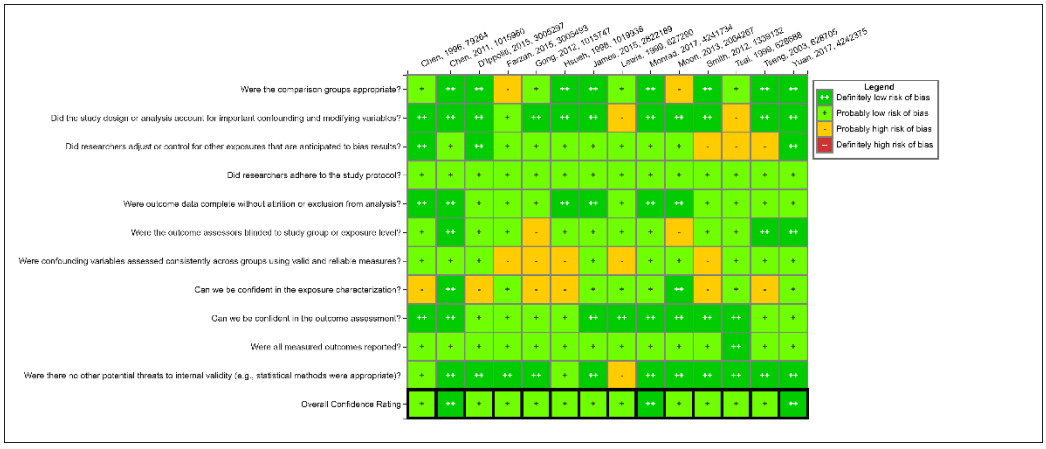


Figure 3-4. Study evaluation ratings for references evaluating ischemic heart disease (see interactive version in HAWC).

Some of the strongest evidence for an association between iAs exposure and IHD-related outcomes comes from prospective cohort and case-control studies with individual-level exposure data. These studies, from multiple countries in populations with different ethnic backgrounds and sociodemographic information, reported positive associations between iAs and IHD incidence and mortality. The consistency of positive findings across multiple studies that applied widely different analytical methods to diverse populations with prior iAs exposures strongly supports a causal relationship between iAs intake and IHD. This includes low-moderate exposure levels, such as the dose-dependent relationship between iAs exposure and IHD morbidity and mortality observed in Italy (D'Ippoliti et al., 2015) and the U.S. (Moon et al., 2013) where a substantial proportion of the population is exposed to iAs concentrations in drinking water that are less than 100 µg/L.

Case-control and cohort studies

The literature review identified 11 case-control and cohort *medium* or *high* confidence studies that evaluated the association between iAs exposure and IHD. Exposure measurements of arsenic included drinking water iAs measurements (Monrad et al., 2017; Lewis et al., 1999; James et al., 2015; Hsueh et al., 1998; Gong and O'Bryant, 2012; D'Ippoliti et al., 2015; Chen et al., 1996), and biomarkers including urine, plasma, and toenail (Yuan et al., 2017; Moon et al., 2013; Farzan et al., 2015a; Chen et al., 2011b), and using both water and biomarker measurements (Chen et al., 2011b).

Large prospective cohort studies reported significant associations between arsenic and IHD incidence and mortality, including a cohort of 3,575 rural American Indian men and women enrolled in the U.S. Strong Heart Study (Moon et al., 2013) and a cohort of 11,746 men and women in Bangladesh enrolled in the Health Effect of Arsenic Longitudinal Study (HEALS) (Chen et al., 2011b). In Moon et al. (2013), when the highest and lowest quartiles of urinary arsenic concentrations (>15.7 vs. <5.8 μg/g creatinine) were compared, the hazard ratio for IHD (coronary heart disease) was 1.71 (95% CI, 1.19 to 2.44; P for trend <0.001) (see Figure 3-5). The authors also found a statistically significant dose-response relationship of urinary arsenic concentrations with IHD incidence and mortality. In the HEALS cohort, Chen et al. (2011b) found a dose-response relation between exposure to arsenic in well water assessed at baseline and mortality from IHD and other heart disease; the hazard ratios in increasing quarters of arsenic concentration in well water (0.1–12.0, 12.1–62.0, 62.1–148.0, and 148.1–864.0 μg/L) were 1.00 (reference), 1.22 (0.65 to 2.32), 1.35 (0.71 to 2.57), and 1.92 (1.07 to 3.43) (P = 0.0019 for trend), respectively (see Figure 3-5). Both studies are limited in that they measured urinary arsenic levels in a single sample at baseline. However, Moon et al. (2013) cited evidence for the temporal stability of arsenic levels in drinking water (Steinmaus et al., 2005; Ryan et al., 2000; Karagas et al., 2001a) and in urine (Navas-Acien et al., 2009b; Karagas et al., 2001a) with long-term constancy in arsenic concentrations for upwards of 10 years. Chen et al. (2011b) observed positive associations of both baseline exposure to iAs in drinking water and concentration in urine with IHD-related mortality.

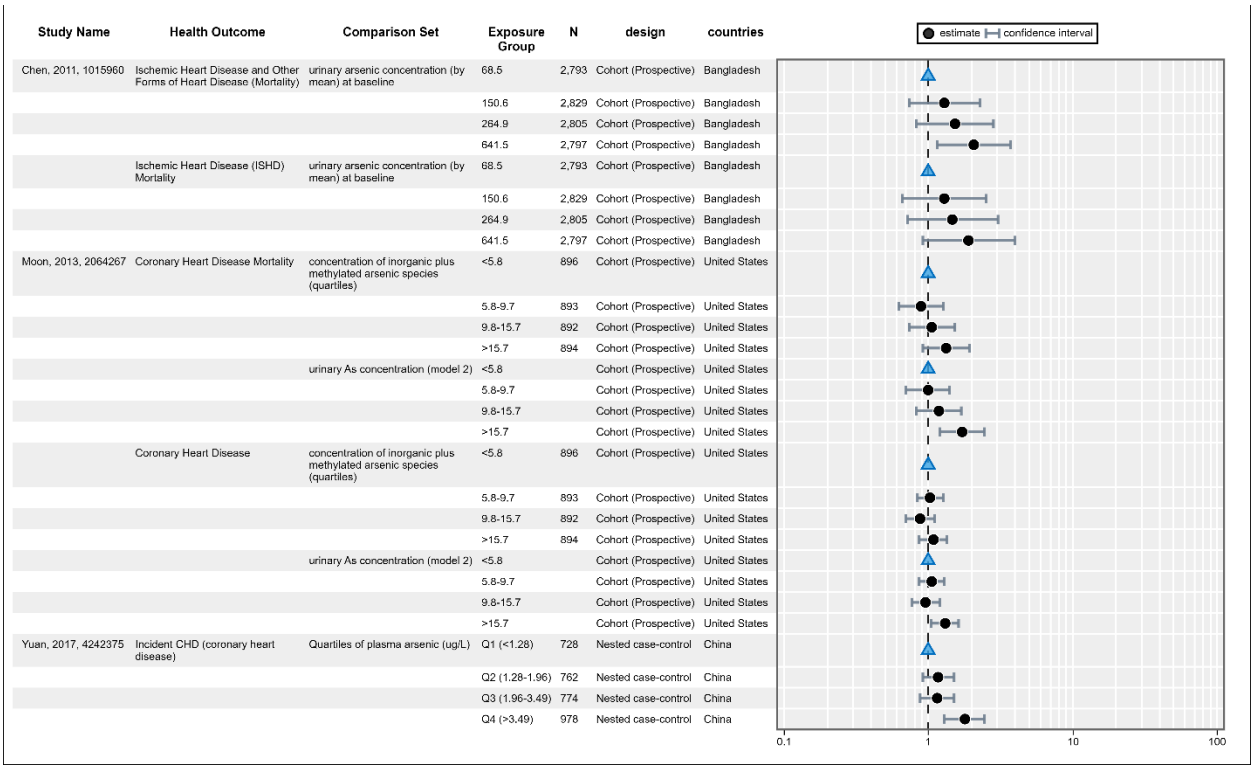
A number of studies examined arsenic exposure using arsenic concentration in well water and duration of drinking water in a highly exposed population of southwestern Taiwan. In Chen et al. (1996), a case-control study, cases were those with Blackfoot disease and controls were without Blackfoot disease, in order to examine IHD mortality. Significant associations with IHD mortality were observed for arsenic-exposure indices, including average arsenic concentration in drinking water and cumulative exposure from drinking artesian well water (relative risks: 2.5, 4.0, and 6.5 for those with cumulative arsenic exposure of 0.1–9.9, 10.0–19.9, and ≥20.0 mg/L-years, respectively, compared with those without arsenic exposure) (Chen et al., 1996). Also in southwestern Taiwan, Hsueh et al. (1998) observed an association between duration of consumption of high arsenic artesian well water and risk of IHD (OR (95% CI): 2.55 (1.02–6.37) and 2.89 (1.01–8.29) for those who consumed the water for 13–29 and ≥30 years, respectively, compared with those who consumed the water for <13 years).

A case-cohort study, which examined exposure to iAs in drinking water using a geospatial model of arsenic concentrations combined with residential histories in the San Luis Valley Diabetes Study in Colorado, U.S. to calculate lifetime exposure (James et al., 2015). The study population (n = 555) was exposed to iAs concentrations in drinking water ranging from 10 to 100 μg/L; hazard ratios were exposure-dependent, increasing with increasing time-weighted average lifetime exposure (IHD risk HR = 1.38, 95% CI: 1.09, 1.78 per 15 μg/L). Consistent results were seen in other studies from the U.S. In Texas, Gong and O'Bryant (2012) used ArcGIS inverse distance weighted interpolation of groundwater concentration in each study participant's home (range: 2.2 – 15.3 μg/L (mean 6.2)), finding that coronary heart disease was associated with low-level arsenic exposure [OR (95% CI): 1.10 (1.00–1.21)]. In a European study that used a similar exposure assessment strategy, D'Ippoliti et al. (2015) followed residents of 17 municipalities in Italy (n = 165,609) to determine the association between iAs exposure and cause-specific mortality. Study participants were followed from 1990 to 2010 and exposed, on average, to 19.3 μg/L for 39.5 years. Metrics indicating average iAs exposure during the first year of residence and cumulative iAs exposure were derived by linking each study participant's geocoded residential history to data on iAs concentration in drinking water. Associations of both exposure metrics with IHD and coronary atherosclerosis were observed in males and in females after adjustment for age, calendar period, socioeconomic status, smoking (municipal-level sales), and radon exposure (municipal level). Monrad et al. (2017) examined the association of 20-year TWA arsenic concentration in drinking water, which was similarly estimated by linking water supply measurements with geocoded residential addresses, and the risk of MI among participants in the Danish Diet, Cancer and Health cohort. The concentration of arsenic levels in drinking water at the participants' baseline address ranged from 0.03 to 25.34 μg/L (median: 0.70 μg/L). No association between 20-year average concentration and MI was observed among the study population overall. An association between ever compared with never living at a residence with ≥10 μg/L was observed, however [IRR: 1.26 (95% CI: 0.89–1.79)].

A toenail biomarker study conducted in the U.S. (Farzan et al., 2015a) provides additional supporting evidence that arsenic is a contributing risk factor for IHD, particularly among long-term smokers. The use of toenails is advantageous in that they reflect inorganic arsenic exposure alone; however, external contamination by iAs that binds to the surface of nails as a result of contact with arsenic in the water prior to or during processing and analysis is a concern (NRC, 1999). Farzan et al. (2015a) conducted a longitudinal analysis of data from the population-based New Hampshire Skin Cancer Study. Investigators measured iAs concentration in toenail clippings (median (range): 0.09 (0–3.26) ppm) to determine the association of iAs exposure with IHD-related mortality. The mean arsenic level in home water supplies of study participants was 2.6 μg/L (range 0–158.1 μg/L). They reported no significant increase in HRs with increasing toenail arsenic concentration with IHD-related mortality for the overall study population after adjusting for skin cancer status, educational attainment, and pack-years of smoking. However, they observed positive associations

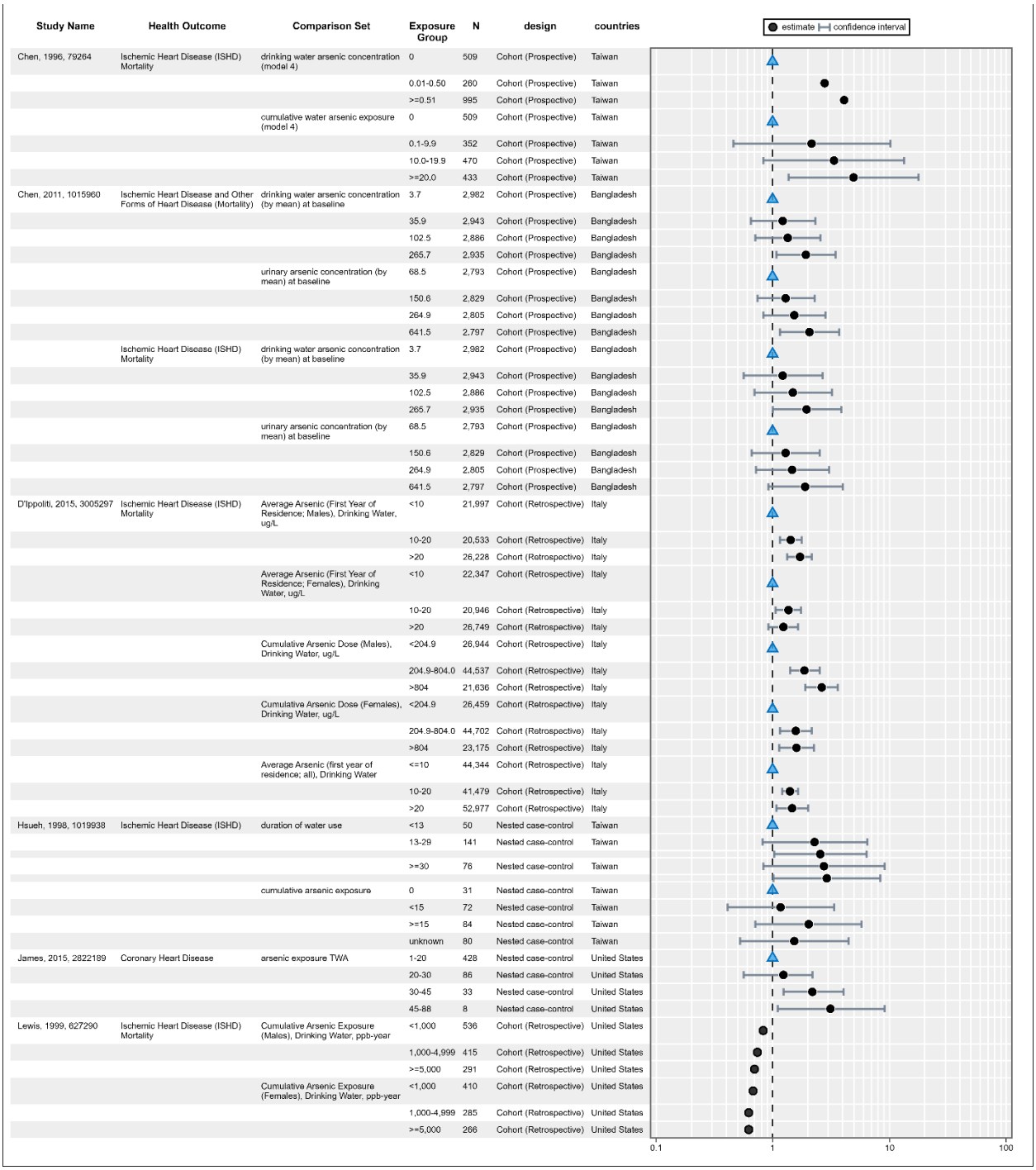
for IHD mortality among current smokers [HR: 1.69 (95% CI: 1.04, 2.75)] and those reporting ≥31 years of smoking [HR: 1.52 (95% CI: 1.02, 2.27)] or ≥30 [HR: 1.66 (95% CI: 1.12, 2.45)] pack-years of smoking. Further, an increasing trend in RRs for toenail arsenic and IHD mortality has been reported for this cohort when grouped into exposure categories of 0.01–0.07 (reference group), 0.07–0.11 [RR: 1.13 (95% CI: 0.77, 1.67)] and 0.11–3.26 [RR: 1.22 (95% CI: 0.82, 1.82)] μg As/g toenail (Moon et al., 2017b).

A nested case-control study of Chinese adults (Dongfeng-Tongji Cohort), Yuan et al. (2017) examined the association of plasma arsenic concentration with incident IHD events (i.e., nonfatal MI, fatal IHD, stable and unstable angina, or coronary revascularization) confirmed by physician adjudication. Blood samples were obtained between 2008 and 2010 and follow-up exams were conducted in 2013. Authors observed a positive association in fully adjusted models [HR 1.78 (95% CI: 1.29, 2.46) comparing the highest to the lowest quartile (>3.49 μg/L vs. <1.28 μg/L) of plasma arsenic concentration].



Study Name	Health Outcome	Comparison Set	Exposure Group	N	design	countries
Chen, 2011, 1015960	Ischemic Heart Disease and Other Forms of Heart Disease (Mortality)	urinary arsenic concentration (by mean) at baseline	68.5	2,793	Cohort (Prospective)	Bangladesh
			150.6	2,829	Cohort (Prospective)	Bangladesh
			264.9	2,805	Cohort (Prospective)	Bangladesh
			641.5	2,797	Cohort (Prospective)	Bangladesh
	Ischemic Heart Disease (ISHD) Mortality	urinary arsenic concentration (by mean) at baseline	68.5	2,793	Cohort (Prospective)	Bangladesh
			150.6	2,829	Cohort (Prospective)	Bangladesh
			264.9	2,805	Cohort (Prospective)	Bangladesh
			641.5	2,797	Cohort (Prospective)	Bangladesh
Moon, 2013, 2064267	Coronary Heart Disease Mortality	concentration of inorganic plus methylated arsenic species (quartiles)	<5.8	896	Cohort (Prospective)	United States
			5.8-9.7	893	Cohort (Prospective)	United States
			9.8-15.7	892	Cohort (Prospective)	United States
			>15.7	894	Cohort (Prospective)	United States
		urinary As concentration (model 2)	<5.8		Cohort (Prospective)	United States
			5.8-9.7		Cohort (Prospective)	United States
			9.8-15.7		Cohort (Prospective)	United States
			>15.7		Cohort (Prospective)	United States
	Coronary Heart Disease	concentration of inorganic plus methylated arsenic species (quartiles)	<5.8	896	Cohort (Prospective)	United States
			5.8-9.7	893	Cohort (Prospective)	United States
			9.8-15.7	892	Cohort (Prospective)	United States
			>15.7	894	Cohort (Prospective)	United States
		urinary As concentration (model 2)	<5.8		Cohort (Prospective)	United States
			5.8-9.7		Cohort (Prospective)	United States
			9.8-15.7		Cohort (Prospective)	United States
			>15.7		Cohort (Prospective)	United States
Yuan, 2017, 4242375	Incident CHD (coronary heart disease)	Quartiles of plasma arsenic (ug/L)	Q1 (<1.28)	728	Nested case-control	China
			Q2 (1.28-1.96)	762	Nested case-control	China
			Q3 (1.96-3.49)	774	Nested case-control	China
			Q4 (>3.49)	978	Nested case-control	China

(a) Ratios measures, biomarkers, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	N	design	countries
Chen, 1996, 79264	Ischemic Heart Disease (ISHD) Mortality	drinking water arsenic concentration (model 4)	0	509	Cohort (Prospective)	Taiwan
			0.01-0.50	260	Cohort (Prospective)	Taiwan
			>=0.51	995	Cohort (Prospective)	Taiwan
		cumulative water arsenic exposure (model 4)	0	509	Cohort (Prospective)	Taiwan
			0.1-9.9	352	Cohort (Prospective)	Taiwan
			10.0-19.9	470	Cohort (Prospective)	Taiwan
			>=20.0	433	Cohort (Prospective)	Taiwan
Chen, 2011, 1015960	Ischemic Heart Disease and Other Forms of Heart Disease (Mortality)	drinking water arsenic concentration (by mean) at baseline	3.7	2,982	Cohort (Prospective)	Bangladesh
			35.9	2,943	Cohort (Prospective)	Bangladesh
			102.5	2,886	Cohort (Prospective)	Bangladesh
			265.7	2,935	Cohort (Prospective)	Bangladesh
		urinary arsenic concentration (by mean) at baseline	68.5	2,793	Cohort (Prospective)	Bangladesh
			150.6	2,829	Cohort (Prospective)	Bangladesh
			264.9	2,805	Cohort (Prospective)	Bangladesh
			641.5	2,797	Cohort (Prospective)	Bangladesh
	Ischemic Heart Disease (ISHD) Mortality	drinking water arsenic concentration (by mean) at baseline	3.7	2,982	Cohort (Prospective)	Bangladesh
			35.9	2,943	Cohort (Prospective)	Bangladesh
			102.5	2,886	Cohort (Prospective)	Bangladesh
			265.7	2,935	Cohort (Prospective)	Bangladesh
		urinary arsenic concentration (by mean) at baseline	68.5	2,793	Cohort (Prospective)	Bangladesh
			150.6	2,829	Cohort (Prospective)	Bangladesh
			264.9	2,805	Cohort (Prospective)	Bangladesh
			641.5	2,797	Cohort (Prospective)	Bangladesh
D'Ippoliti, 2015, 3005297	Ischemic Heart Disease (ISHD) Mortality	Average Arsenic (First Year of Residence; Males), Drinking Water, ug/L	<10	21,997	Cohort (Retrospective)	Italy
			10-20	20,533	Cohort (Retrospective)	Italy
			>20	26,228	Cohort (Retrospective)	Italy
		Average Arsenic (First Year of Residence; Females), Drinking Water, ug/L	<10	22,347	Cohort (Retrospective)	Italy
			10-20	20,946	Cohort (Retrospective)	Italy
			>20	26,749	Cohort (Retrospective)	Italy
		Cumulative Arsenic Dose (Males), Drinking Water, ug/L	<204.9	26,944	Cohort (Retrospective)	Italy
			204.9-804.0	44,537	Cohort (Retrospective)	Italy
			>804	21,636	Cohort (Retrospective)	Italy
		Cumulative Arsenic Dose (Females), Drinking Water, ug/L	<204.9	26,459	Cohort (Retrospective)	Italy
			204.9-804.0	44,702	Cohort (Retrospective)	Italy
			>804	23,175	Cohort (Retrospective)	Italy
		Average Arsenic (first year of residence; all), Drinking Water	<=10	44,344	Cohort (Retrospective)	Italy
			10-20	41,479	Cohort (Retrospective)	Italy
			>20	52,977	Cohort (Retrospective)	Italy
Hsueh, 1998, 1019938	Ischemic Heart Disease (ISHD)	duration of water use	<13	50	Nested case-control	Taiwan
			13-29	141	Nested case-control	Taiwan
			>=30	76	Nested case-control	Taiwan
		cumulative arsenic exposure	0	31	Nested case-control	Taiwan
			<15	72	Nested case-control	Taiwan
			>=15	84	Nested case-control	Taiwan
			unknown	80	Nested case-control	Taiwan
James, 2015, 2822189	Coronary Heart Disease	arsenic exposure TWA	1-20	428	Nested case-control	United States
			20-30	86	Nested case-control	United States
			30-45	33	Nested case-control	United States
			45-88	8	Nested case-control	United States
Lewis, 1999, 627290	Ischemic Heart Disease (ISHD) Mortality	Cumulative Arsenic Exposure (Males), Drinking Water, ppb-year	<1,000	536	Cohort (Retrospective)	United States
			1,000-4,999	415	Cohort (Retrospective)	United States
			>=5,000	291	Cohort (Retrospective)	United States
		Cumulative Arsenic Exposure (Females), Drinking Water, ppb-year	<1,000	410	Cohort (Retrospective)	United States
			1,000-4,999	285	Cohort (Retrospective)	United States
			>=5,000	266	Cohort (Retrospective)	United States

(b) Ratio measures, drinking water, categorical exposure

Figure 3-5. Thumbnail schematic of case-control and cohort studies examining the association between IHD and inorganic arsenic exposure (a) ratio measures, biomarkers, categorical exposure, (b) ratio measures, drinking water, categorical exposure (see interactive data graphics).

Cross-sectional studies

One cross-sectional study of *medium* confidence examined the association between arsenic exposure and IHD (Tseng et al., 2003). In the U.S., Tseng et al. (2003) found OR (95% CI) for IHD was 3.60 (1.11, 11.65) for those with ≥15.0 mg/L-years consuming artesian well water, when compared with those with zero years of consuming artesian well water.

Ecological studies

Two ecological studies of *medium* confidence were included, which examined IHD-related mortality (Tsai et al., 1999; Smith et al., 2012). In Taiwan, Tsai et al. (1999), observed a statistically significant positive association for IHD mortality for both males (SMR: 1.75, 95% CI: 1.59–1.92) and females (SMR: 1.44, 95% CI: 1.27–1.61) (median arsenic in artesian wells = 780 ppb). Statistically significant positive associations were observed for acute myocardial infarction mortality in Chile (Smith et al., 2012).

Natural experiment: Highly exposed population in southwest Taiwan

Studies mentioned here have been discussed previously in their respective study design sections and are also briefly discussed here together for additional context. The studies reporting the strongest exposure-dependent positive associations examined the effect of cumulative arsenic exposure ([mg/L*yr]) on IHD-related morbidity or mortality in the southwestern coastal region of Taiwan, where chronic arsenic poisoning was endemic (Tseng et al., 2003; Tsai et al., 1999; Hsueh et al., 1998; Chen et al., 1996). The average drinking water concentrations in the U.S. are 500-fold lower, with even the highest concentrations observed 10- to 100-fold lower than those within the Taiwan study population Residents of Southwest Taiwan were exposed to arsenic in drinking water at concentrations of 700–930 µg/L over decades, until the use of drinking water wells containing high concentrations of arsenic was discontinued in the mid-1970s. Community level interventions to stop use of these wells created natural experiments. Some ecological studies also included unique design features that took advantage of natural experiments with exposure periods having documented beginnings, endings, or both, allowing for examination of pre- and post-intervention cardiovascular mortality rates.

Supplemental information: Meta-analyses

Moon et al. (2017b) updated prior meta-analyses of CVD health outcomes by Moon et al. (2012)[12] and Navas-Acien et al. (2006). The Moon et al. (2017b) meta-analyses used criteria

[12]The Moon et al. (2017b) meta-analysis is discussed further in Appendix C.1.2 (Ischemic Heart Disease (IHD) Incidence; Comparison of Studies Selected for EPA Dose-Response Meta-Analysis and Studies Used in Earlier Meta-Analyses). EPA's Bayesian meta-regression analyses of CVD and IHD outcomes are summarized in Section 4.3.7. There are important differences between the Moon et al. (2017b); Moon et al. (2012), and the EPA meta-analyses of CVD and IHD outcomes with respect to study selection, data adjustments/pre-analysis and modeling methods.

including from the Newcastle-Ottawa Scale to assess study quality to estimate the relationship between levels of arsenic in drinking water and relative risks for incidence of and fatality from clinical CVD endpoints (all CVD, CHD, and stroke) in the adult general population. They excluded studies of childhood exposures, occupational exposures uncommon in the general population (e.g., arsenic trioxide), case reports or case series, preclinical CVD outcomes, ecological studies (or studies analyzed as group-level data), studies with prevalent outcomes, and studies that reported results with fewer than three exposure categories. Their approach was similar to EPA's dose-response meta-analysis (see Section 4.3.7). Moon et al. (2017b)[13] reported the summary effect estimates in these meta-analyses, which supported a positive association between chronic high levels of arsenic in drinking water and IHD. Compared with 10 mg/l, the estimated pooled relative risks [95% confidence interval (CI)] for 20 mg/l water arsenic were 1.11 (1.05, 1.17) for CHD incidence, and 1.16 (1.07, 1.26) for CHD mortality.

Summary

Overall, epidemiological studies provide robust evidence for exposure-dependent associations between arsenic exposure and both IHD incidence and mortality. As discussed in the protocol (link provided in Appendix A) and supported by the NASEM (NASEM, 2019), this is consistent with associations noted in other assessments (ATSDR, 2007; ATSDR, 2016; WHO, 2011b; WHO, 2011a). The study designs most informative to this question, prospective cohort and case-control studies with individual-level exposure data from multiple countries in populations with different ethnic backgrounds and sociodemographic information, demonstrate consistently elevated IHD in association with iAs exposure. At least one dose-response gradient association was observed in almost every study, covering both incidence and mortality, (Yuan et al., 2017; Moon et al., 2013; James et al., 2015; Hsueh et al., 1998; D'Ippoliti et al., 2015; Chen et al., 1996; Chen et al., 2011b), and large effect estimates that gain statistical significance at higher exposure levels, with many studies conducted in areas with lower levels of drinking water arsenic exposure (<100 µg/L (including <20 µg/L)). Further supporting these findings are cross-sectional and ecological studies, "natural experiment" studies from southwest Taiwan, and meta-analyses.

Cardiovascular Disease

The literature review identified 12 epidemiological studies that were considered *medium* or *high* confidence that evaluated the association between iAs exposure and cardiovascular disease and mortality. Cardiovascular disease was identified by methods including review of hospitalization or death records adjudicated by expert committee, and death certificates verified for ICD coding by

[13]Moon et al. (2012); Moon et al. (2017b) reported that "compared with 10 mg/L, the estimated pooled relative risks [95% confidence interval (CI)] for 20 mg/l water arsenic, based on a log-linear model, were 1.09 (1.03, 1.14) (N=2) for CVD incidence, 1.07 (1.01, 1.14) (N=6) for CVD mortality, 1.11 (1.05, 1.17) (N=4) for CHD incidence, 1.16 (1.07, 1.26) (N=6) for CHD mortality, 1.08 (0.99, 1.17) (N=2) for stroke incidence and 1.06 (0.93, 1.20) (N=6) for stroke mortality."

a nosologist. All eligible studies that reported effect estimates (see Section 1.6.3) are summarized in Figure 3-6.

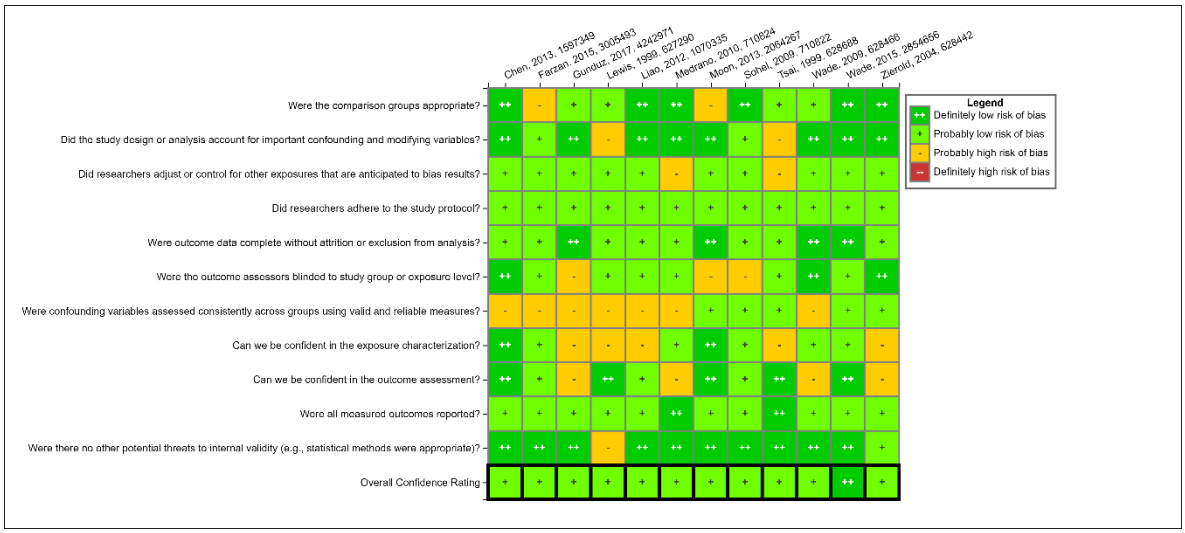


Figure 3-6. Study evaluation ratings for references evaluating cardiovascular disease (see interactive version in HAWC).

Case-control and cohort studies

The literature review identified eight case-control and cohort *medium* or *high* confidence studies (Wade et al., 2009; Wade et al., 2015; Sohel et al., 2009; Moon et al., 2013; Liao et al., 2012; Lewis et al., 1999; Farzan et al., 2015a; Chen et al., 2013c) that evaluated the association between iAs exposure and cardiovascular disease. Exposure measurements of arsenic included drinking water iAs measurements (Lewis et al., 1999; Wade et al., 2009; Sohel et al., 2009; Liao et al., 2012; Wade et al., 2015); biomarkers including urine, hair, and toenail (Chen et al., 2013c; Moon et al., 2013; Wade et al., 2015; Farzan et al., 2015a), and using both water and biomarker measurements (Wade et al., 2015; Chen et al., 2013c).

Two large prospective cohort studies with urinary arsenic concentrations, a cohort of 3,575 rural American Indian men and women enrolled in the U.S. Strong Heart Study (Moon et al., 2013) and a cohort of 11,746 men and women in Bangladesh enrolled in the Health Effect of Arsenic Longitudinal Study (HEALS) (Chen et al., 2011b), reported significant associations with CVD incidence and mortality and total arsenic or its metabolites. In the Strong Heart Study, Moon et al. (2013) found chronic exposure to arsenic was associated with CVD incidence and mortality. When the highest and lowest quartiles of arsenic concentrations (>15.7 vs. <5.8 μg/g creatinine) were compared in Moon et al. (2013), the hazard ratio for cardiovascular disease was 1.65 (95% CI, 1.20 to 2.27; P for trend <0.001) (see Figure 3-7b). The authors also found a statistically significant dose-response relationship of urinary arsenic concentrations with CVD incidence and mortality. Chen et al. (2011b) found changes in urinary arsenic over time were positively associated with risk of mortality from total cardiovascular disease. There was a dose-response relationship between

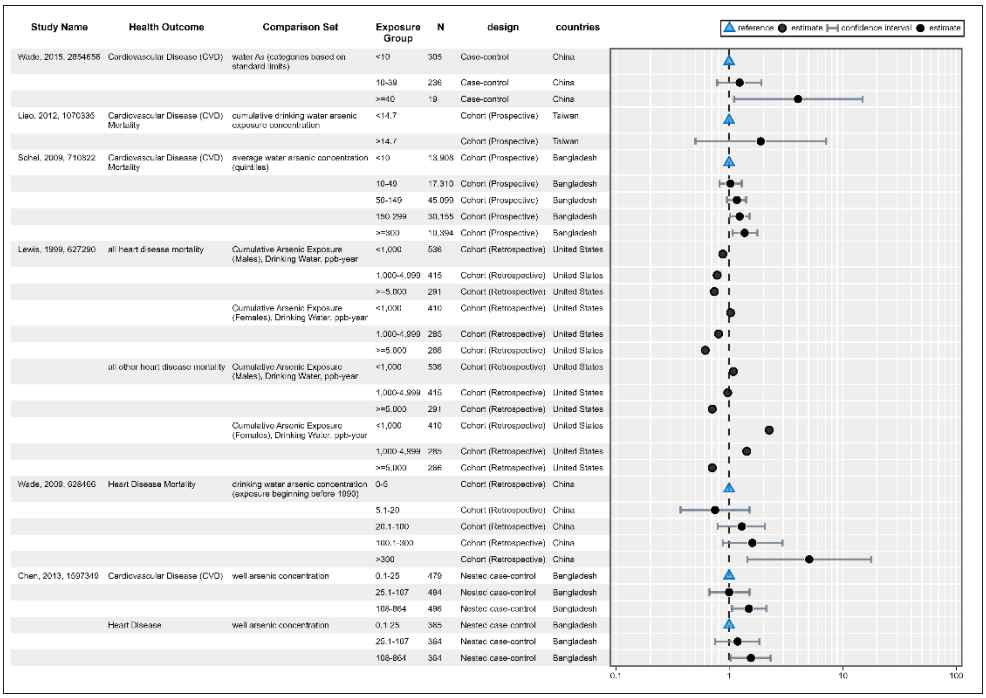
exposure to arsenic in well water (mean = 63.5 μg/L), which was also measured in HEALS, assessed at baseline and mortality from heart disease. Also conducted in HEALS, a case-cohort analysis (well arsenic range: 0.1–864 μg/L) reported increased risk of CVD-related mortality among those with lower methylation capacity (Chen et al., 2013c).

In the highly exposed population of southwestern Taiwan (artesian well water arsenic concentration range: 35–1140 ppm; median 780 ppm), an association was reported between cumulative arsenic exposure (ppm-years) and abnormal lactate dehydrogenase activity, a marker of CVD risk (Liao et al., 2012).

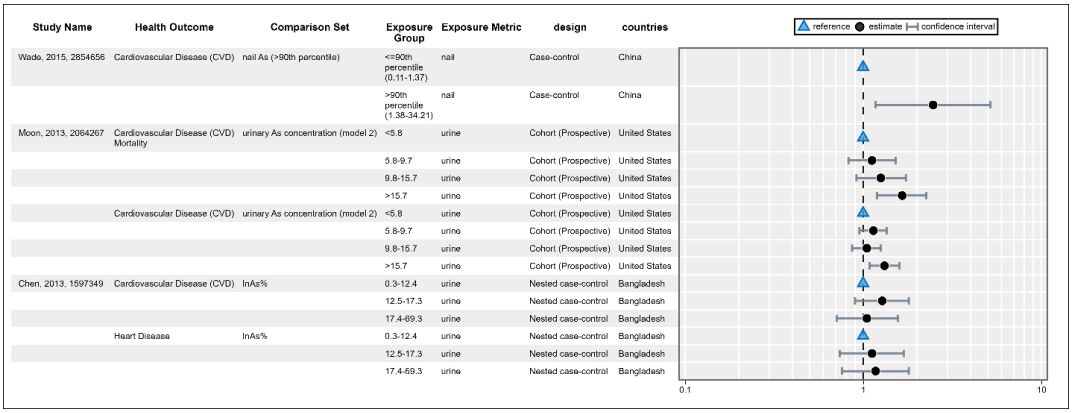
Studies examining drinking water arsenic concentrations from other countries were consistent with the southwestern Taiwan findings. In a cohort from an Inner Mongolian village, heart disease mortality was observed to be associated with arsenic exposure, as measured by well water arsenic exposure among those exposed for 10–20 years (Wade et al., 2009). In Bangladesh, similar findings of excess mortality due to cardiovascular disease were seen (Sohel et al., 2009).

In the U.S., in Utah, Lewis et al. (1999) used residence history and median drinking water arsenic concentration (range: 14 – 166 μg/L), authors observed increased mortality from hypertensive heart disease.

In a toenail biomarker assessment, Wade et al. (2015) conducted a hospital-based, case-control study in Inner Mongolia using arsenic concentrations in toenail clippings and arsenic concentration measured at each participant's primary drinking water source as exposure metrics. As shown in Figure 3-7, arsenic concentrations in drinking water and toenails were associated with increased CVD incidence. The drinking water arsenic concentration ranged from less than the limit of detection (average 0.16 μg/g) to 208 μg/L (mean 8.9 μg/L) among study participants.



(a) Ratio measures, drinking water, categorical exposure



(b) Ratio measures, biomarkers, categorical exposure

Figure 3-7. Thumbnail schematic of case-control and cohort studies with CVD outcomes in relation to inorganic arsenic exposure (a) ratio measures, drinking water, categorical exposure, (b) ratio measures, biomarkers, categorical exposure (see interactive data graphics).

Cross-sectional studies

Two cross-sectional studies of *medium* confidence examined the association between arsenic exposure and CVD outcomes in Turkey and Taiwan, respectively (Gunduz et al., 2017; Zierold et al., 2004). Both received a *deficient* rating for the exposure assessment domain due to concerns over using self-collected water samples, self-reported residential history, and self-reported duration of well water consumption as surrogates for exposure. However, since the

exposures to arsenic from drinking water were shown to be long-term, there is confidence in the temporality of exposure and disease occurrence. Zierold et al. (2004) found a statistically significant association between water arsenic exposure (As >10 µg/L compared with As <2 µg/L) and heart attack (OR (95% CI): 2.08 (1.10, 4.31)). Gunduz et al. (2017) examined the distribution of chronic diseases in villages with high arsenic levels in drinking water supplies in Turkey (range: 27–177.2 µg/L) and found diseases of the circulatory system to have the highest prevalence compared to other chronic diseases (including diseases of the nervous system; respiratory system; digestive system; musculoskeletal system).

Ecological studies

Two ecological studies of *medium* confidence were included, examining CVD-related mortality in Taiwan, and Spain, respectively (see Figure 3-8) (Tsai et al., 1999; Medrano et al., 2010). Statistically significant positive associations were observed for heart disease mortality in Taiwan (median arsenic in artesian wells = 780 ppb) and CVD mortality in Spain (mean municipal drinking water arsenic concentrations ranged from <1 to 199 µg/L).

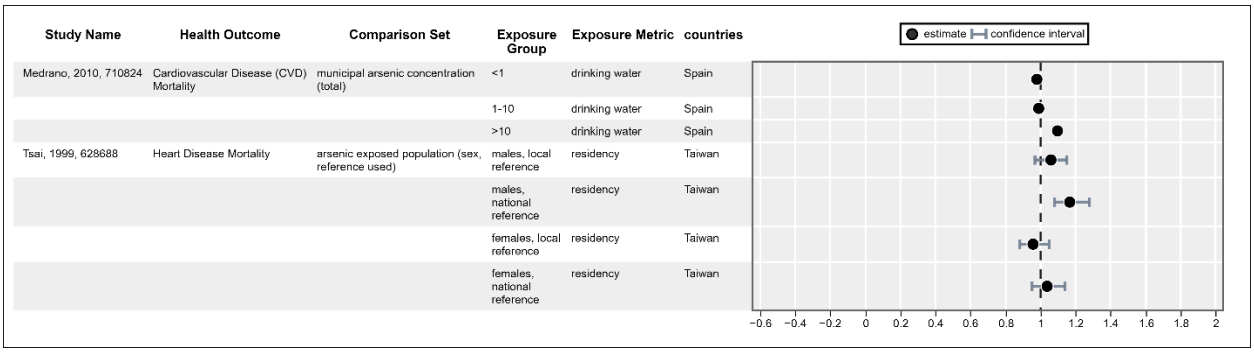


Figure 3-8. Thumbnail schematic of ecological epidemiological studies addressing the association between iAs exposure and CVD mortality (see interactive data graphic).

Supplemental information: Meta-analyses

Moon et al. (2017b) updated prior meta-analyses of CVD health outcomes by Moon et al. (2012)[14] and Navas-Acien et al. (2006). The Moon et al. (2017b) meta-analyses used criteria including from the Newcastle-Ottawa Scale to assess study quality to estimate the relationship between levels of arsenic in drinking water and relative risks for incidence of and fatality from clinical CVD endpoints (all CVD, CHD, and stroke) in the adult general population. They excluded

[14]The Moon et al. (2017b) meta-analysis is discussed further in Appendix C.1.2 (Ischemic Heart Disease (IHD) Incidence; Comparison of Studies Selected for EPA Dose-Response Meta-Analysis and Studies Used in Earlier Meta-Analyses). EPA's Bayesian meta-regression analyses of CVD and IHD outcomes are summarized in Section 4.3.7. There are important differences between the Moon et al. (2012); Moon et al. (2017b) and the EPA meta-analyses of CVD and IHD outcomes with respect to study selection, data adjustments/pre-analysis and modeling methods.

studies of childhood exposures, occupational exposures uncommon in the general population (e.g., arsenic trioxide), case reports or case series, preclinical CVD outcomes, ecological studies (or studies analyzed as group-level data), studies with prevalent outcomes, and studies that reported results with fewer than three exposure categories. Their approach was similar to EPA's dose-response meta-analysis (see Section 4.3.7). Moon et al. (2017b)[15] reported the summary effect estimates in these meta-analyses, which supported a positive association between chronic high levels of arsenic in drinking water and multiple CVD endpoints (all CVD, stroke). Compared with 10 μg/l, the estimated pooled relative risks [95% confidence interval (CI)] for 20 μg/l water arsenic were 1.09 (1.03, 1.14) for CVD incidence, 1.07 (1.01, 1.14) for CVD mortality, and 1.08 (0.99, 1.17) for stroke incidence.

Summary

Overall, epidemiological studies provide robust evidence for exposure-dependent associations between arsenic exposure and cardiovascular disease. As discussed in the protocol (link provided in Appendix A) and supported by the (NASEM, 2019), this is consistent with associations noted in other assessments (ATSDR, 2007; ATSDR, 2016; WHO, 2011b; WHO, 2011a). The study designs most informative to this question, prospective cohort and case-control studies with individual-level exposure data from multiple countries in populations with different ethnic backgrounds and sociodemographic information, demonstrate consistently elevated CVD-related outcomes in association with iAs exposure, dose-response gradient associations observed in some studies [e.g., (Wade et al., 2015; Moon et al., 2013; Medrano et al., 2010; Chen et al., 2013c)], large effect estimates that gain statistical significance at higher exposure levels, and coherence across markers of disease. Further supporting these findings are cross-sectional studies, ecological studies, and meta-analyses.

Intermediate Endpoints and/or Risk Factors for Ischemic Heart Disease and Cardiovascular Disease

This section describes the consistent associations that have been observed between arsenic exposure and intermediate endpoints that are evaluated when making a CVD or IHD diagnosis. Studies will be discussed by study design under each intermediate endpoints reviewed: hypertension, atherosclerosis, and electrocardiogram abnormalities.

[15] Moon et al. (2012); Moon et al. (2017b) reported that "compared with 10 μg/L, the estimated pooled relative risks [95% confidence interval (CI)] for 20 μg/l water arsenic, based on a log-linear model, were 1.09 (1.03, 1.14) (N=2) for CVD incidence, 1.07 (1.01, 1.14) (N=6) for CVD mortality, 1.11 (1.05, 1.17) (N=4) for CHD incidence, 1.16 (1.07, 1.26) (N=6) for CHD mortality, 1.08 (0.99, 1.17) (N=2) for stroke incidence and 1.06 (0.93, 1.20) (N=6) for stroke mortality."

Hypertension and increased blood pressure

The literature review identified 31 epidemiological studies, 12 case-control/cohort (Yu et al., 2017; Wang et al., 2011; Rahman et al., 1999; Newman et al., 2016; Lewis et al., 1999; Jiang et al., 2015; Huang et al., 2007; Hawkesworth et al., 2013; Hall et al., 2017; Gong and O'Bryant, 2012; Farzan et al., 2015b; Farzan et al., 2015c) and 19 cross-sectional studies (Zierold et al., 2004; Wei et al., 2017b; Wei et al., 2017a; Skröder et al., 2015; Rahman and Axelson, 2001; Osorio-Yáñez et al., 2015; Li et al., 2013b; Li et al., 2013a; Li et al., 2015; Kwok et al., 2007; Kunrath et al., 2013; Jones et al., 2011; Islam et al., 2012a; Hossain et al., 2017; Guha Mazumder et al., 2012; Chen et al., 1995; Chen et al., 2007; Chen et al., 2012b; Ameer et al., 2015), considered *medium* or *high* confidence that evaluated the association between iAs exposure and hypertension (see Figure 3-9). Hypertension is usually defined as systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg. The condition can promote left ventricular hypertrophy and heart failure and is a risk factor for CHD and stroke. Studies also examine changes in SBP, DBP and pulse pressure, which is the difference between SBP and DBP and a risk factor for heart disease and stroke. The results from studies of hypertension are summarized in Figure 3-10 and Figure 3-11.

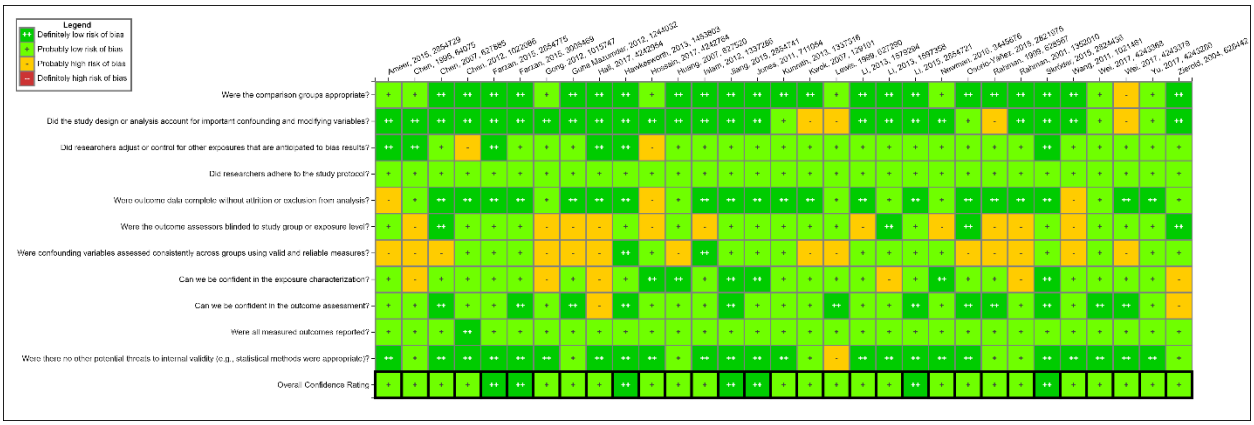
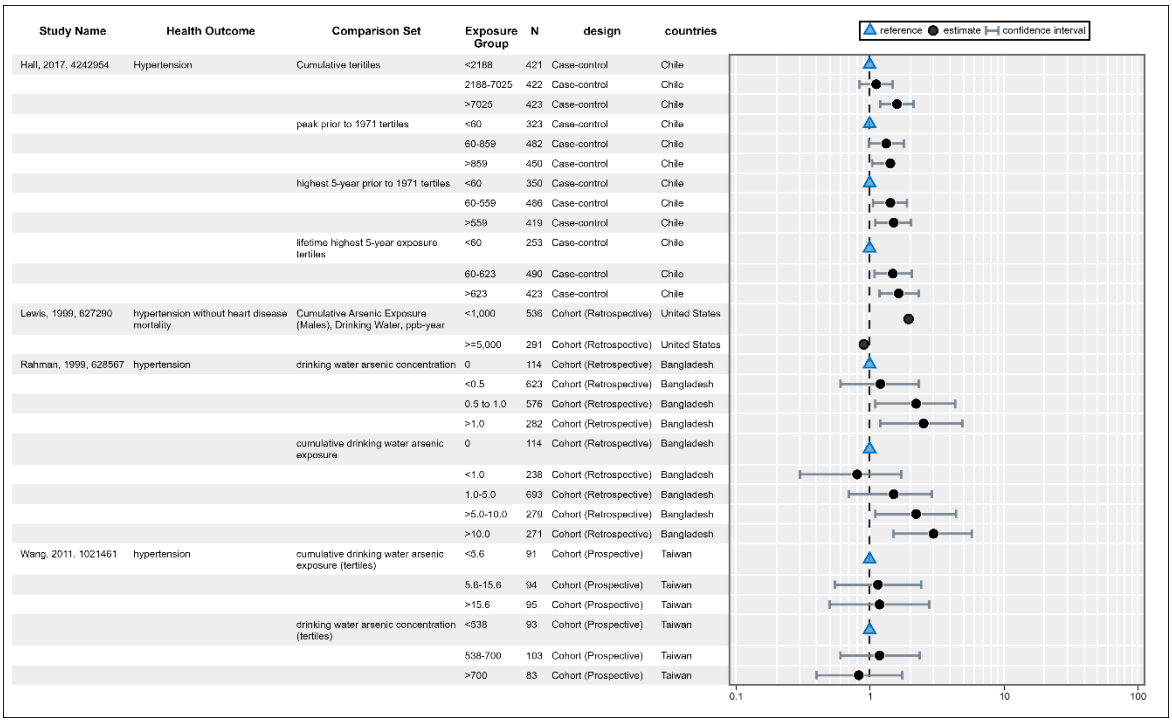


Figure 3-9. Study evaluation ratings for references evaluating hypertension and increased blood pressure (see interactive version in HAWC).

Since hypertension can resolve in the absence of exposure the studies included in the plot below should be interpreted in the context of the temporal relationship of the exposure (e.g., the appropriateness of the exposure metric) and the ascertainment of the outcome. While prospective cohort studies are generally better able to establish temporality, cross-sectional studies were found to be informative for blood pressure effects associated with concurrent exposures to arsenic. Many cross-sectional studies were able to infer temporality in that arsenic exposure was relatively stable over time, such as in drinking water and urinary arsenic samples (median(IQR): 8.3 µg/L (4.2–17.1)) in the U.S. (NHANES) (Jones et al., 2011), and in southwest Taiwan where long-term exposure was identified by sampling in previously-Blackfoot disease endemic areas (median

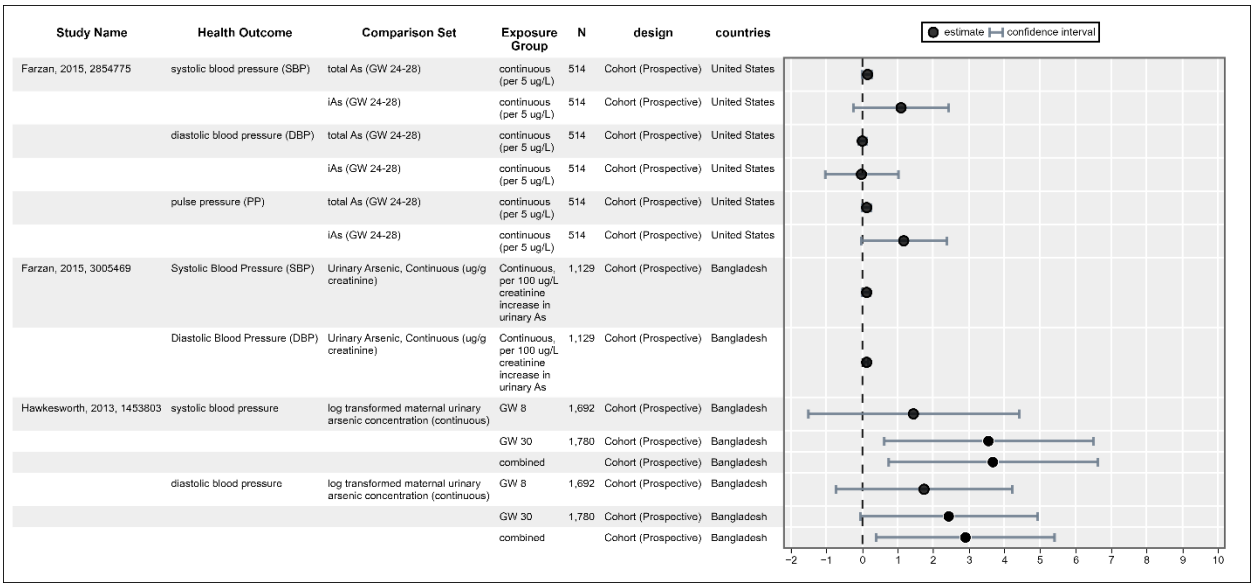
arsenic concentration of the artesian well water ranged from: 700–930 μg/L) (Chen et al., 1995) (see Figure 3-11).

Several studies examined the relationship between inorganic arsenic exposure and hypertension in cohorts in Bangladesh. In a retrospective cohort analysis, both water concentrations (i.e., >50 μg/L) and cumulative arsenic concentration (i.e., >5 mg-y/L) were associated with hypertension in four villages in the districts of Faridpur, Nawabgong, Bangladesh, Jessore, and Narayongong (Rahman et al., 1999) (see Figure 3-10). Although arsenic concentrations were not measured and assigned to individuals in this study, previous measurements indicated that more than 50% of wells had arsenic concentrations greater than 50 μg/L and eligible participants (≥30 years old) were exposed for their entire lifetime. Further, in a subsequent cross-sectional analysis of this cohort (drinking water arsenic concentration range: nondetectable – 2040 μg/L) the risk of hypertension was higher among those with skin lesions related to arsenic exposures compared with those without skin lesions (Rahman and Axelson, 2001). By contrast, in a cross-sectional study conducted in other areas of Bangladesh (i.e., Comilla, Jhenidah, Kalinganj districts) where arsenic concentrations in drinking water ranged from 10–1,400 μg/L, Islam et al. (2012a) reported an association of arsenic exposure with pulse pressure (PP) but not with hypertension (see Figure 3-13). In another cross-sectional study, Hossain et al. (2017) observed chronic arsenic drinking water exposure (mean(SD): 17.76 μg/L (15.16)) inversely associated with LINE-1 methylation levels, which may be involved with elevated BP. Additional analyses focusing on sensitive subgroups and subclinical increases in blood pressure (e.g., SBP, DBP, and pulse pressure [PP]) are discussed below and provide additional context for the main effects observed in the hypertension studies.



Study Name	Health Outcome	Comparison Set	Exposure Group	N	design	countries
Hall, 2017, 4242954	Hypertension	Cumulative tertiles	<2188	421	Case-control	Chile
			2188-7025	422	Case-control	Chile
			>7025	423	Case-control	Chile
		peak prior to 1971 tertiles	<60	323	Case-control	Chile
			60-859	482	Case-control	Chile
			>859	450	Case-control	Chile
		highest 5-year prior to 1971 tertiles	<60	350	Case-control	Chile
			60-559	486	Case-control	Chile
			>559	419	Case-control	Chile
		lifetime highest 5-year exposure tertiles	<60	253	Case-control	Chile
			60-623	490	Case-control	Chile
			>623	423	Case-control	Chile
Lewis, 1999, 627290	hypertension without heart disease mortality	Cumulative Arsenic Exposure (Males), Drinking Water, ppb-year	<1,000	536	Cohort (Retrospective)	United States
			>=5,000	291	Cohort (Retrospective)	United States
Rahman, 1999, 628567	hypertension	drinking water arsenic concentration	0	114	Cohort (Retrospective)	Bangladesh
			<0.5	623	Cohort (Retrospective)	Bangladesh
			0.5 to 1.0	576	Cohort (Retrospective)	Bangladesh
			>1.0	282	Cohort (Retrospective)	Bangladesh
		cumulative drinking water arsenic exposure	0	114	Cohort (Retrospective)	Bangladesh
			<1.0	238	Cohort (Retrospective)	Bangladesh
			1.0-5.0	693	Cohort (Retrospective)	Bangladesh
			>5.0-10.0	279	Cohort (Retrospective)	Bangladesh
			>10.0	271	Cohort (Retrospective)	Bangladesh
Wang, 2011, 1021461	hypertension	cumulative drinking water arsenic exposure (tertiles)	<5.6	91	Cohort (Prospective)	Taiwan
			5.6-15.6	94	Cohort (Prospective)	Taiwan
			>15.6	95	Cohort (Prospective)	Taiwan
		drinking water arsenic concentration (tertiles)	<538	93	Cohort (Prospective)	Taiwan
			538-700	103	Cohort (Prospective)	Taiwan
			>700	83	Cohort (Prospective)	Taiwan

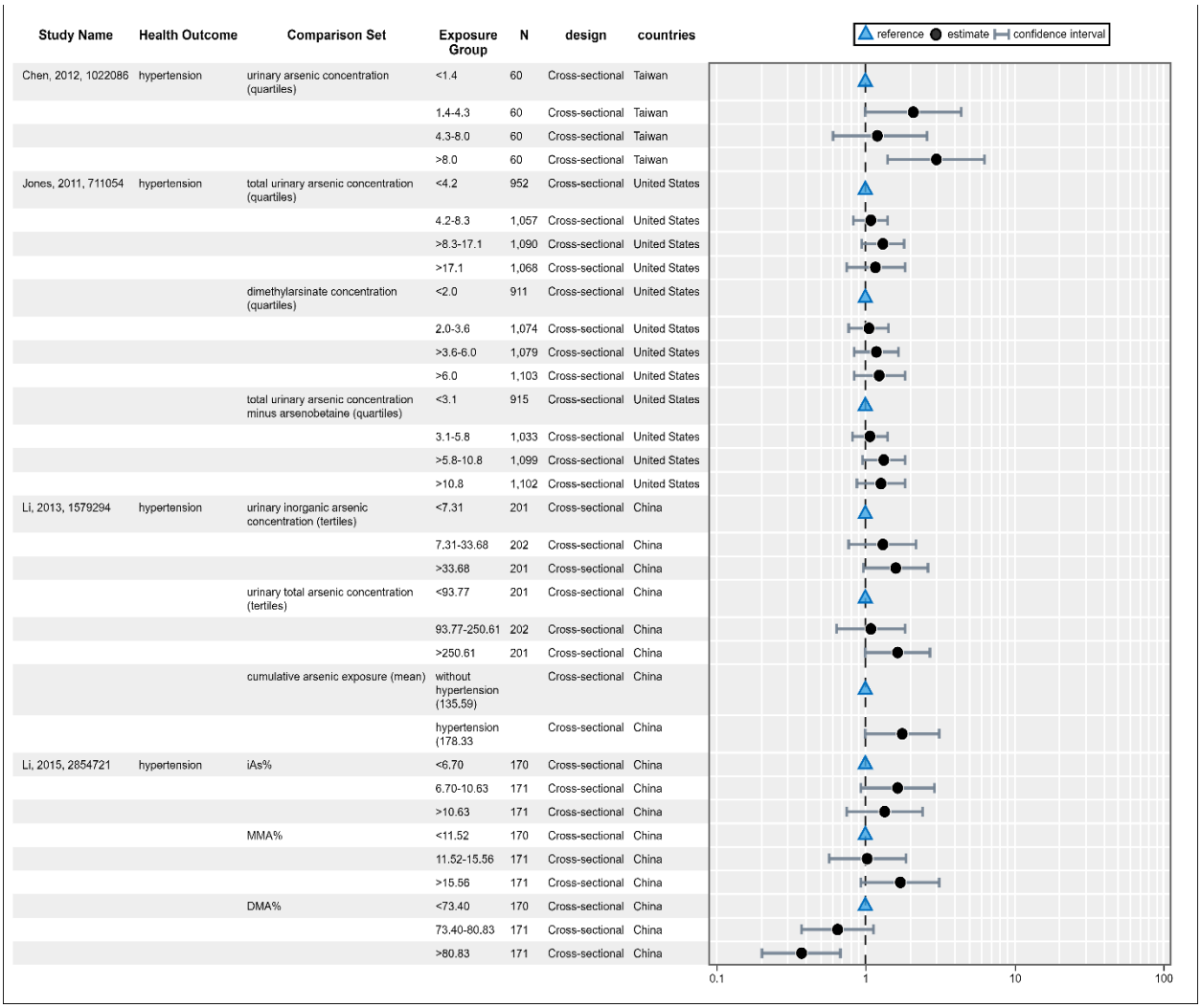
(a) Ratio measures, drinking water, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	N	design	countries
Farzan, 2015, 2854775	systolic blood pressure (SBP)	total As (GW 24-28)	continuous (per 5 ug/L)	514	Cohort (Prospective)	United States
		iAs (GW 24-28)	continuous (per 5 ug/L)	514	Cohort (Prospective)	United States
	diastolic blood pressure (DBP)	total As (GW 24-28)	continuous (per 5 ug/L)	514	Cohort (Prospective)	United States
		iAs (GW 24-28)	continuous (per 5 ug/L)	514	Cohort (Prospective)	United States
	pulse pressure (PP)	total As (GW 24-28)	continuous (per 5 ug/L)	514	Cohort (Prospective)	United States
		iAs (GW 24-28)	continuous (per 5 ug/L)	514	Cohort (Prospective)	United States
Farzan, 2015, 3005469	Systolic Blood Pressure (SBP)	Urinary Arsenic, Continuous (ug/g creatinine)	Continuous, per 100 ug/L creatinine increase in urinary As	1,129	Cohort (Prospective)	Bangladesh
	Diastolic Blood Pressure (DBP)	Urinary Arsenic, Continuous (ug/g creatinine)	Continuous, per 100 ug/L creatinine increase in urinary As	1,129	Cohort (Prospective)	Bangladesh
Hawkesworth, 2013, 1453803	systolic blood pressure	log transformed maternal urinary arsenic concentration (continuous)	GW 8	1,692	Cohort (Prospective)	Bangladesh
			GW 30	1,780	Cohort (Prospective)	Bangladesh
			combined		Cohort (Prospective)	Bangladesh
	diastolic blood pressure	log transformed maternal urinary arsenic concentration (continuous)	GW 8	1,692	Cohort (Prospective)	Bangladesh
			GW 30	1,780	Cohort (Prospective)	Bangladesh
			combined		Cohort (Prospective)	Bangladesh

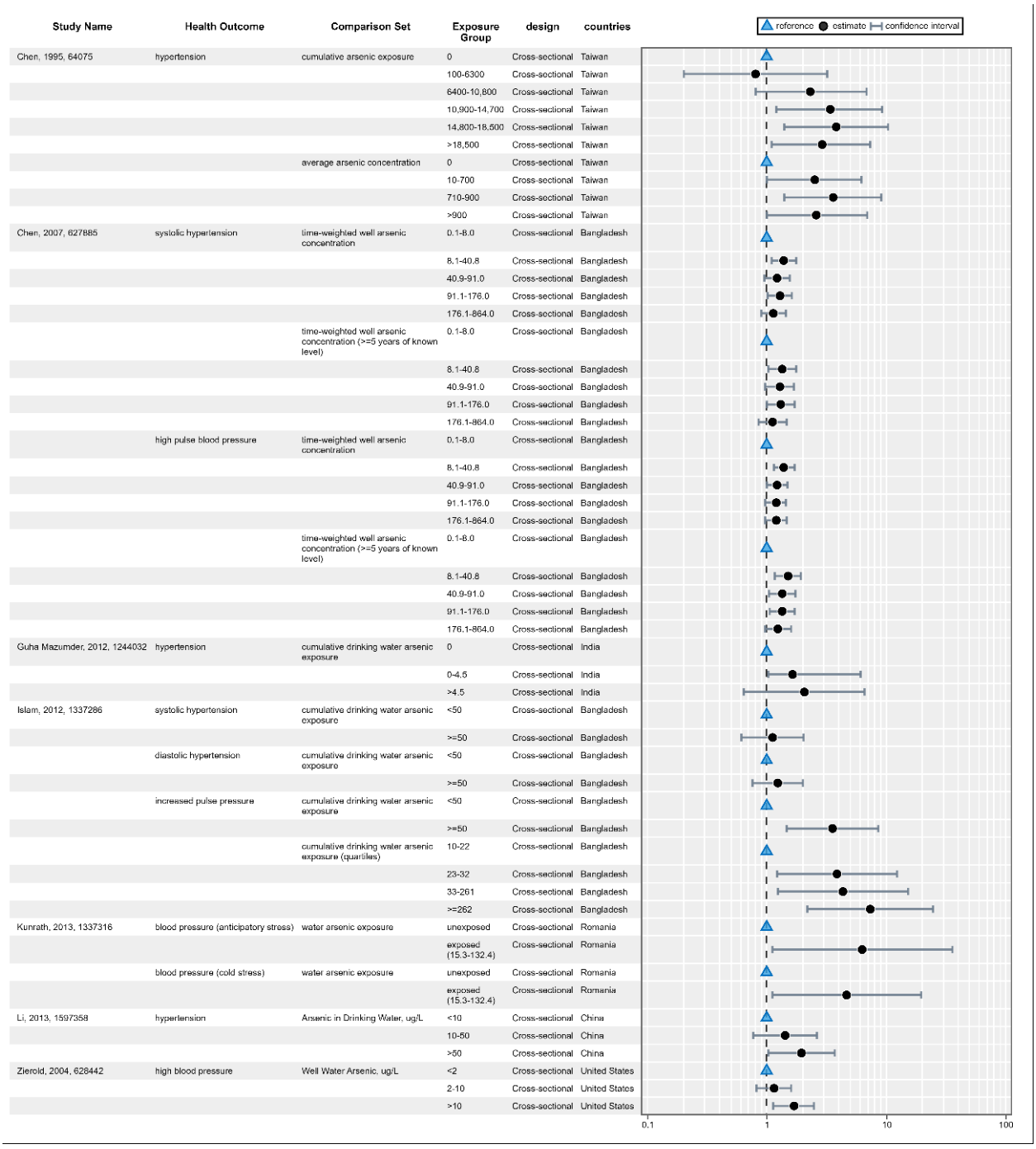
(b) Difference measures, urine, continuous exposure

Figure 3-10. Thumbnail schematic of case-control/cohort studies of hypertension in response to inorganic arsenic exposure (a) ratio measures, drinking water, categorical exposure; (b) difference measures, urine, continuous exposure (see interactive data graphic).



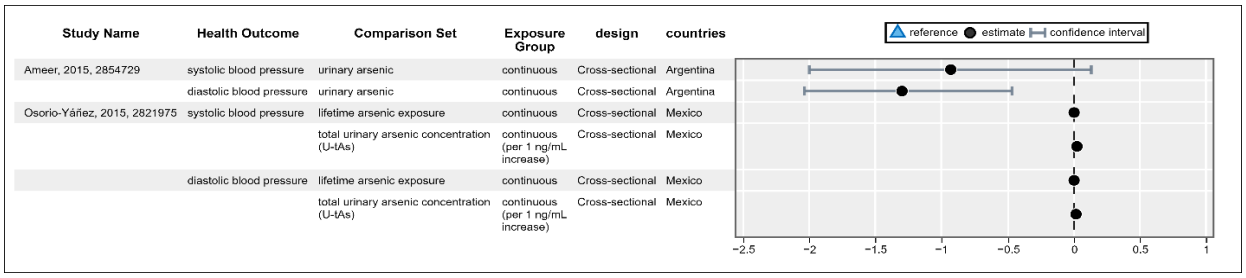
Study Name	Health Outcome	Comparison Set	Exposure Group	N	design	countries
Chen, 2012, 1022086	hypertension	urinary arsenic concentration (quartiles)	<1.4	60	Cross-sectional	Taiwan
			1.4-4.3	60	Cross-sectional	Taiwan
			4.3-8.0	60	Cross-sectional	Taiwan
			>8.0	60	Cross-sectional	Taiwan
Jones, 2011, 711054	hypertension	total urinary arsenic concentration (quartiles)	<4.2	952	Cross-sectional	United States
			4.2-8.3	1,057	Cross-sectional	United States
			>8.3-17.1	1,090	Cross-sectional	United States
			>17.1	1,068	Cross-sectional	United States
		dimethylarsinate concentration (quartiles)	<2.0	911	Cross-sectional	United States
			2.0-3.6	1,074	Cross-sectional	United States
			>3.6-6.0	1,079	Cross-sectional	United States
			>6.0	1,103	Cross-sectional	United States
		total urinary arsenic concentration minus arsenobetaine (quartiles)	<3.1	915	Cross-sectional	United States
			3.1-5.8	1,033	Cross-sectional	United States
			>5.8-10.8	1,099	Cross-sectional	United States
			>10.8	1,102	Cross-sectional	United States
Li, 2013, 1579294	hypertension	urinary inorganic arsenic concentration (tertiles)	<7.31	201	Cross-sectional	China
			7.31-33.68	202	Cross-sectional	China
			>33.68	201	Cross-sectional	China
		urinary total arsenic concentration (tertiles)	<93.77	201	Cross-sectional	China
			93.77-250.61	202	Cross-sectional	China
			>250.61	201	Cross-sectional	China
		cumulative arsenic exposure (mean)	without hypertension (135.59)		Cross-sectional	China
			hypertension (178.33		Cross-sectional	China
Li, 2015, 2854721	hypertension	iAs%	<6.70	170	Cross-sectional	China
			6.70-10.63	171	Cross-sectional	China
			>10.63	171	Cross-sectional	China
		MMA%	<11.52	170	Cross-sectional	China
			11.52-15.56	171	Cross-sectional	China
			>15.56	171	Cross-sectional	China
		DMA%	<73.40	170	Cross-sectional	China
			73.40-80.83	171	Cross-sectional	China
			>80.83	171	Cross-sectional	China

(a) Ratio measures, urine, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	design	countries
Chen, 1995, 64075	hypertension	cumulative arsenic exposure	0	Cross-sectional	Taiwan
			100-6300	Cross-sectional	Taiwan
			6400-10,800	Cross-sectional	Taiwan
			10,900-14,700	Cross-sectional	Taiwan
			14,800-18,500	Cross-sectional	Taiwan
			>18,500	Cross-sectional	Taiwan
		average arsenic concentration	0	Cross-sectional	Taiwan
			10-700	Cross-sectional	Taiwan
			710-900	Cross-sectional	Taiwan
			>900	Cross-sectional	Taiwan
Chen, 2007, 627885	systolic hypertension	time-weighted well arsenic concentration	0.1-8.0	Cross-sectional	Bangladesh
			8.1-40.8	Cross-sectional	Bangladesh
			40.9-91.0	Cross-sectional	Bangladesh
			91.1-176.0	Cross-sectional	Bangladesh
			176.1-864.0	Cross-sectional	Bangladesh
		time-weighted well arsenic concentration (>=5 years of known level)	0.1-8.0	Cross-sectional	Bangladesh
			8.1-40.8	Cross-sectional	Bangladesh
			40.9-91.0	Cross-sectional	Bangladesh
			91.1-176.0	Cross-sectional	Bangladesh
			176.1-864.0	Cross-sectional	Bangladesh
	high pulse blood pressure	time-weighted well arsenic concentration	0.1-8.0	Cross-sectional	Bangladesh
			8.1-40.8	Cross-sectional	Bangladesh
			40.9-91.0	Cross-sectional	Bangladesh
			91.1-176.0	Cross-sectional	Bangladesh
			176.1-864.0	Cross-sectional	Bangladesh
		time-weighted well arsenic concentration (>=5 years of known level)	0.1-8.0	Cross-sectional	Bangladesh
			8.1-40.8	Cross-sectional	Bangladesh
			40.9-91.0	Cross-sectional	Bangladesh
			91.1-176.0	Cross-sectional	Bangladesh
			176.1-864.0	Cross-sectional	Bangladesh
Guha Mazumder, 2012, 1244032	hypertension	cumulative drinking water arsenic exposure	0	Cross-sectional	India
			0-4.5	Cross-sectional	India
			>4.5	Cross-sectional	India
Islam, 2012, 1337286	systolic hypertension	cumulative drinking water arsenic exposure	<50	Cross-sectional	Bangladesh
			>=50	Cross-sectional	Bangladesh
	diastolic hypertension	cumulative drinking water arsenic exposure	<50	Cross-sectional	Bangladesh
			>=50	Cross-sectional	Bangladesh
	increased pulse pressure	cumulative drinking water arsenic exposure	<50	Cross-sectional	Bangladesh
			>=50	Cross-sectional	Bangladesh
		cumulative drinking water arsenic exposure (quartiles)	10-22	Cross-sectional	Bangladesh
			23-32	Cross-sectional	Bangladesh
			33-261	Cross-sectional	Bangladesh
			>=262	Cross-sectional	Bangladesh
Kunrath, 2013, 1337316	blood pressure (anticipatory stress)	water arsenic exposure	unexposed	Cross-sectional	Romania
			exposed (15.3-132.4)	Cross-sectional	Romania
	blood pressure (cold stress)	water arsenic exposure	unexposed	Cross-sectional	Romania
			exposed (15.3-132.4)	Cross-sectional	Romania
Li, 2013, 1597358	hypertension	Arsenic in Drinking Water, ug/L	<10	Cross-sectional	China
			10-50	Cross-sectional	China
			>50	Cross-sectional	China
Zierold, 2004, 628442	high blood pressure	Well Water Arsenic, ug/L	<2	Cross-sectional	United States
			2-10	Cross-sectional	United States
			>10	Cross-sectional	United States

(b) Ratio measures, drinking water, categorical exposure



(c) Difference measures, urine, continuous exposure

Figure 3-11. Thumbnail schematic of cross-sectional studies of hypertension in response to inorganic arsenic exposure (a) ratio measures, urine, categorical exposure; (b) ratio measures, drinking water, categorical exposure; (c) difference measures, urine, continuous exposure (see interactive data graphics).

In Bangladesh, the association of inorganic arsenic exposure and hypertension was examined in a cross-sectional study among participants in the HEALS cohort, a large study (n = 11,746) of adults (≥18 years old) who lived in the study area for at least 5 years. Water samples and location data were collected for approximately 6,000 wells in the study area, and individual-level data on a large number of covariates including nutritional status were ascertained. No association of time-weighted average exposure to arsenic (range: 0.1–864.0 µg/L) with general hypertension was reported among HEALS participants (Chen et al., 2007) (see Figure 3-13). Associations with PP were observed, however, and subgroup analyses indicated that effect of arsenic on blood pressure was discernable among those with longer-duration exposures (≥5 years to known concentrations of iAs in drinking water) and lower nutrient intake (e.g., vitamin B and folate). Subsequent analyses of the data from this cohort reported associations of baseline concentration of arsenic in water (median: 62 µg/L) and arsenic concentration in urine (median: 88 µg/L) with small statistically significant annual increases in both SBP and DBP (Jiang et al., 2015). Wei et al. (2017b) reported an increase in SBP and DBP in association with cumulative arsenic exposure (range: <10–824.70 µg/L) in Inner Mongolia, China. Modification of the longitudinal association of water arsenic concentration with blood pressure (well water arsenic in those with normal (<120 mm Hg) SBP, mean(SD): 102.0 (115.9); well water arsenic in those pre-hypertensive to hypertensive (≥120 mm Hg), mean(SD): 91.9 (104.5) by genes related to methylation capacity, oxidative stress, and endothelial dysfunction was also observed among HEALS participants (Farzan et al., 2015c). Wei et al. (2017a) further reported a higher prevalence of hypertension among those with arsenic-associated skin lesions compared with those without arsenic-associated skin lesions in Inner Mongolia, China (water arsenic concentrations ranged from (means) 114.00–203.77 µg/L across skin lesion groups) (see Figure 3-13).

Hall et al. (2017) used data from a population-based case-control study of cancer in northern Chile to conduct an analysis of the relationship between highest lifetime 5-year average arsenic concentration and hypertension (self-reported physician diagnosed hypertension or use of

anti-hypertensive medications ascertained between 2007 and 2010). Study participants may have been exposed to concentrations greater than 860 μg/L in drinking water prior to the implementation of alternative drinking water sources in the 1970s. Arsenic exposure was positively associated with hypertension in this study [OR: 1.49 (95% CI: 1.09, 2.05) and 1.65 (95% CI: 1.18, 2.32), comparing the middle and upper tertile of 5-year average arsenic concentration to the reference category of <60 μg/L]. Arsenic exposure estimated based on the sum of arsenic metabolite concentrations in urine, was associated with decreased SBP and DBP among women (18–65 years of age) in northern Argentina (Ameer et al., 2015), however. Concentrations of arsenic in drinking water ranged from 10 to 200 μg/L in the villages studied.

The association of inorganic arsenic exposure with hypertension was also studied in several cohorts in northern China (Inner Mongolia). Li et al. (2013a) found dose-dependent associations between iAs in water and prevalent hypertension (OR: 1.47 (0.767, 2.618) comparing group with water concentrations from 10–50 μg/L to the reference category (i.e., <10 μg/L) and OR: 1.94 (95% CI: 1.018, 3.687) comparing the group with >50 μg/L to the reference in adjusted models (see Figure 3-13). Participants in this study were recruited from villages where interventions to reduce arsenic exposure in drinking water had not occurred and concentrations ranged from 0–760 μg/L. Consistent findings were also seen in an additional Chinese cohort, which observed an association between hair arsenic concentration and hypertension risk (Yu et al., 2017). An exposure-dependent pattern of associations was shown in another cohort in Inner Mongolia [OR: 1.204(95% CI: 0.632, 2.292) and OR: 1.871(95% CI: 1.022, 3.424) comparing the second (0.10–0.35 mg/L-year) and third (>0.35 mg/L) tertiles to the reference category (<0.10 mg/L-year), respectively] (Li et al., 2013b) (see Figure 3-13). A similar pattern of associations of iAs and iAs % in urine and hypertension were observed, and low methylation capacity indicated by a higher percentage of monomethylarsonic acid (MMA) in urine was also associated with hypertension in another Inner Mongolia, China study from this author (Li et al., 2015). In Taiwan, exposure to high levels of arsenic in artesian well water was associated with hypertension (Wang et al., 2011).

Finally, U.S. studies show positive associations with markers of arsenic exposure in urine (Jones et al., 2011) and drinking water concentrations greater than 10 that were estimated by linking ground water arsenic concentrations to geocoded residential address (Gong and O'Bryant, 2012). Jones et al. (2011) examined a representative U.S. population of participants in the National Health and Nutrition Examination Survey [NHANES], reporting a null associations per doubling of total iAs in urine (categorical results presented in Figure 3-13). A positive association of DMA with hypertension (OR: 1.11 (95% CI: 0.99–1.24] per doubling) was observed, however. GIS estimated arsenic concentrations in drinking water (range: 2.2–15.3 μg/L (mean 6.2)) was associated with hypertension (OR: 1.10 [95% CI: 1.03, 1.17]) in a study in rural Texas where arsenic concentrations have been found to be elevated (Gong and O'Bryant, 2012). In another cross-sectional study, Kunrath et al. (2013) reported stress-induced increases in both SBP and DBP associated with drinking water arsenic exposure (mean: 40.2 μg/L) in normotensive men in Romania (see Figure 3-

13). This finding is consistent with a role for sympathetic hyperreactivity in arsenic-associated hypertension risk. Additional U.S. studies observed an association between urinary arsenic concentration (median(IQR): 9.9 μg/g creatinine (6.0–15.7)) and peripheral arterial disease markers in American Indians (Newman et al., 2016); arsenic in drinking water (range: 14–166 μg/L) and mortality from hypertensive heart disease in residents from Utah (Lewis et al., 1999); and arsenic in private well water (range: 14–166 μg/L) and high blood pressure (Zierold et al., 2004).

Supplemental information: Meta-analysis

Abir et al. (2012) conducted a meta-analysis examining the relationship between chronic arsenic exposure and hypertension. Seven cross-sectional studies and one cohort study that met their inclusion criteria were analyzed. On the basis of pooling of extracted odds ratios for the highest and lowest exposure categories in each study, they reported an OR of 1.9 (95% CI: 1.2–3.0) when using arsenic concentration in drinking water as the exposure metric, and an OR of 1.4 (95% CI: 0.95–2.0) when using arsenic concentration and duration as the exposure metric. These two meta-analyses provide evidence for a relationship between arsenic exposure and hypertension, although limited by imprecision due to the small sample sizes and heterogeneity in effect estimates across studies.

Pregnancy and early childhood exposures

Several studies examined the effect of exposure to iAs during pregnancy or early childhood on blood pressure. In a prospective cohort study of pregnant women in New Hampshire (well water concentration mean(SD): 4.3(11.0) μg/L), each 5 μg/L increase in urinary As concentration at baseline was associated with a 0.15 mmHg (95% CI: 0.02, 0.29) increase in systolic blood pressure per month and a 0.14 mmHg (95% CI: 0.02, 0.25) increase in pulse pressure per month (Farzan et al., 2015b). No association with DBP was observed. Farzan et al. (2015b) derived several metrics to indicate methylation capacity (i.e., concentration of MMA and dimethylarsenic acid [DMA] in urine, which are indices of primary and secondary methylation) but did not report strong evidence that the effect of arsenic exposure was increased among those with lower methylation capacity. In a study conducted among women of reproductive age in Inner Mongolia, Kwok et al. (2007) reported that higher SBP and DBP were associated with increasing quartiles of arsenic concentration (≤20 [reference group], 21–50, 51–100, and >100 μg/L) in drinking water. DBP increased by a smaller increment than SBP did for the same quartile increase of arsenic concentration. Information on potential confounders was unavailable for more than half the study population, however, and potential confounding was indicated in a sensitivity analysis comparing results for those with and without covariate information.

Hawkesworth et al. (2013) conducted a follow-up study of children in rural Bangladesh to evaluate the effect of nutrient supplementation on birth outcomes. The sum of iAs and its metabolites in urine during early (weeks 8–12) and late (weeks 30–33) gestation and in infants 18

months of age was assessed relative to blood pressure at 4.5 years of age. Each 1 mg/L of urinary arsenic during gestation was associated with increased SBP (3.69 mmHg [95% CI: 0.74–6.63] per mg/L increase in urinary arsenic) and DBP (2.91 mmHg [95% CI: 0.41–5.42]). A 1 mg/L urinary arsenic concentration at 18 months of age (median (IQR): 33.9 μg/L (18.2, 77.4)) was associated with an 8.25 mmHg (95% CI: 1.37, 15.1; p = 0.02) increase in systolic blood pressure at 4.5 years. The study authors did not find any interaction with nutrient supplementation. However, in a subsequent cross-sectional study based on children from the same cohort, no associations of current urinary arsenic (median (IQR): 54 μg/L (16, 343)) with SBP and DBP were observed in multivariable models simultaneously adjusted for cadmium and selenium (Skröder et al., 2015). This differs from the previous observation for this cohort. The change could be due to ongoing exposure mitigation in the area, decreased sensitivity of this age group and/or the model adjustment for cadmium and selenium (Skröder et al., 2015), both of which showed a slight positive association with increasing SPB and DPB. Osorio-Yáñez et al. (2015) reported cross-sectional associations of total arsenic concentration in urine with increased SBP and DBP among children 3–8 years of age in Mexico. In addition, duration of water consumption was associated with increased left ventricular mass in this study, providing further indirect support for arsenic-associated changes in blood pressure. In 2009, drinking water arsenic concentrations ranged from 3 to 135 μg/L in the study area. From 1993 to 2009, the iAs concentrations in the water ranged from 3 to 398 μg/L. Study subjects were recruited in 2009.

Summary

Exposure-dependent associations of arsenic exposure (drinking water concentrations, cumulative exposure, and biomarkers or arsenic or its metabolites in urine) with prevalent hypertension are generally observed across epidemiologic studies. A dose-response gradient was observed in many studies [e.g., (Zierold et al., 2004; Wang et al., 2011; Rahman et al., 1999; Li et al., 2013b; Li et al., 2013a; Li et al., 2015; Jones et al., 2011; Islam et al., 2012a; Hawkesworth et al., 2013; Hall et al., 2017; Guha Mazumder et al., 2012)]. This evidence indicates that the effect of arsenic exposure on hypertension and blood pressure might be more pronounced among those with higher exposure (>100 μg/L), longer-duration exposures, lower methylation capacity, or lower nutrient intake. Studies also show consistent associations with increased systolic blood pressure or pulse pressure in adults, pregnant women, and children.

Atherosclerosis

The literature review identified 16 epidemiological studies, 6 case-control/cohort (Wu et al., 2006; Wu et al., 2010b; Wang et al., 2002; Wang et al., 2007; Wang et al., 2010; Hsieh et al., 2008b) and 10 cross-sectional studies (Wang et al., 2009; Velmurugan et al., 2018; Stea et al., 2016; Osorio-Yáñez et al., 2013; Nong et al., 2016; Mateen et al., 2017; Li et al., 2009; Chiou et al., 2001b; Chen et al., 2006; Chen et al., 2013b), considered *medium* or *high* confidence that evaluated the association between iAs exposure and atherosclerosis (see Figure 3-12). Coronary atherosclerosis

is typically clinically assessed using ultrasonography to measure cIMT where a cIMT ≥1 mm or the presence of observable plaque is typically considered atherosclerosis. However, different definitions of atherosclerosis are used in the iAs evidence base and atherosclerosis severity might or might not have been classified.

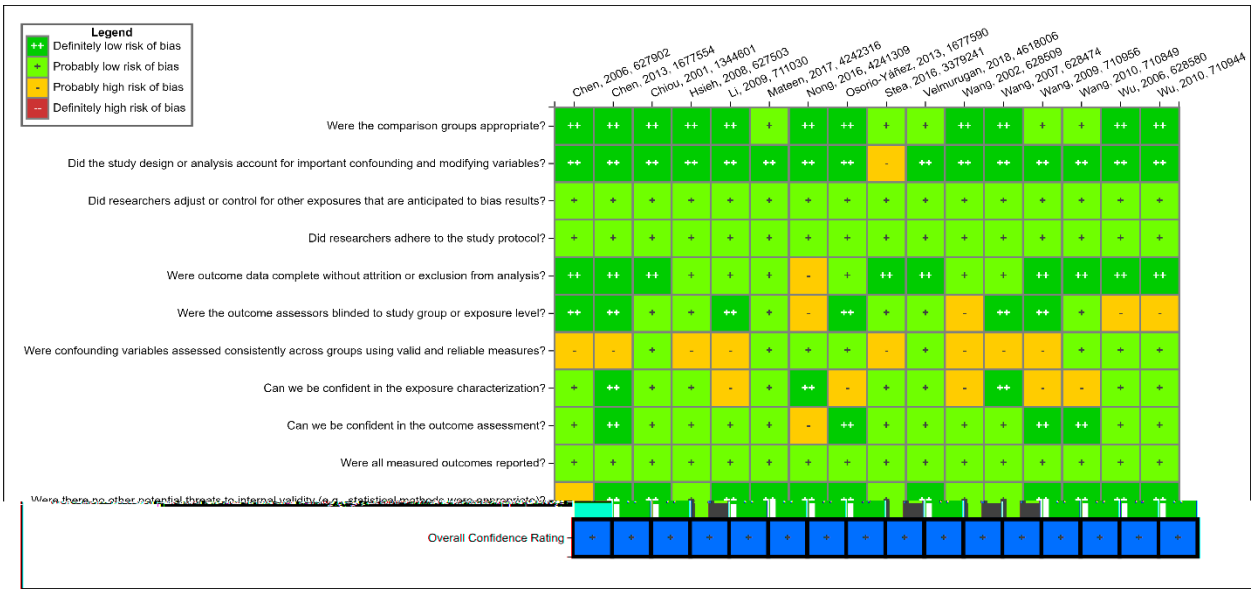
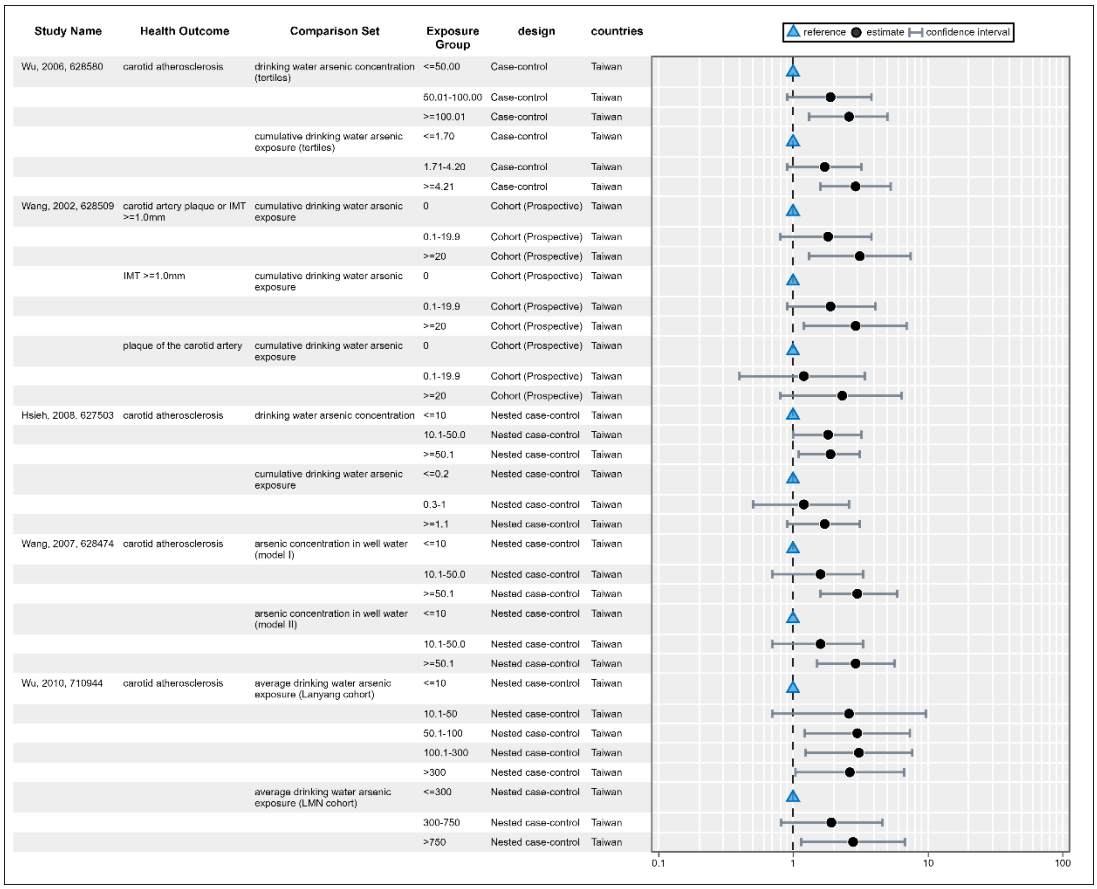


Figure 3-12. Study evaluation ratings for references evaluating atherosclerosis (see interactive version in HAWC).

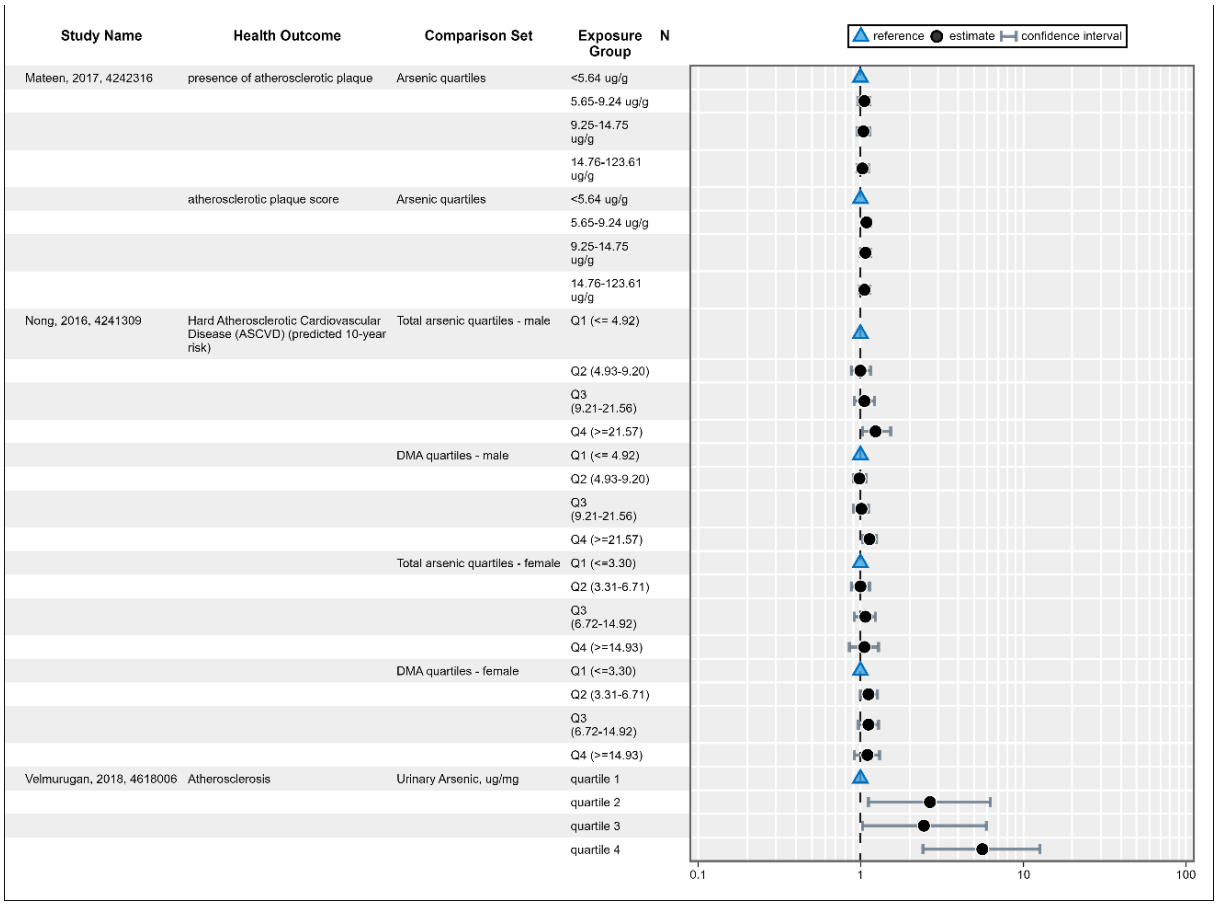
The epidemiological studies presented in Figure 3-13 and Figure 3-14 report generally consistent exposure-dependent associations for iAs with atherosclerosis. Cumulative exposure to iAs among the highly exposed (700–930 µg/L iAs in drinking water for decades) cohort residing in southwestern Taiwan was associated with carotid atherosclerosis indicated by cIMT (Wang et al., 2002). A relationship between arsenic and cIMT also has been observed in populations with lower exposures. Mateen et al. (2017) studied the association of baseline arsenic concentration in urine (sum of inorganic and methylated species) with several measures of atherosclerosis measured after follow-up among American Indians enrolled in the Strong Heart Study (SHS). Moon et al. (2013) described the concentrations of arsenic in drinking water for this cohort, which ranged from less than 10 to 61 µg/L. The mean difference in cIMT was 0.01 mm (95% CI: 0.00, 0.02 mm) comparing the 80th versus the 20th percentile of urine arsenic concentration. They also observed cIMT increases in exposure group quartiles 2 (5.65–9.24 µg/g creatinine), 3 (9.25–14.75 µg/g creatinine) and 4 (14.76–123.61 µg/g creatinine) of 0.01 (95% CI: −0.01, 0.02), 0.01 (95% CI: 0.00, 0.03) and 0.01 (95% CI: 0.00, 0.04), respectively. A borderline positive association with the presence of plaque was observed [RR: 1.04 (95% CI: 0.99, 1.09] also comparing the 80th versus the 20th percentile urine arsenic concentrations. Chen et al. (2013b) reported a 5.1-mm (95% CI: 0.2–10.3) increase in cIMT per standard deviation (SD) increase in baseline concentration of iAs in water (mean: 81.1 µg/L) and an 11.7-mm (95% CI: 1.8–21.6) increase in cIMT per SD increase in baseline

urinary iAs concentration (mean: 259.5 µg/g) in the HEALS cohort. In this cohort, a sizeable proportion of the population is exposed to low or moderate arsenic in drinking water (median: 41 µg/L, 90th percentile 225 µg/L). The effect of arsenic exposure on cIMT thickness was greater among those with lower methylation capacity, indicated by arsenic metabolites in urine, and among smokers. Although associations were not exposure-dependent in a study by Chiou et al. (2001b), both water concentration and cumulative iAs exposure were associated with carotid atherosclerosis among the population of northeastern Taiwan, where the concentration in drinking water ranged from 0 to >3,000 µg/L. Atherosclerosis was associated with water arsenic concentrations (OR = 2.13, 95% CI: 1.04–4.32 comparing those with exposure ranging from 50–99.9 µg/L to those in the reference category of <50 µg/L). Urinary arsenic concentration was associated with cIMT ≥1 mm in a cross-sectional analysis of participants in a study of residents in a farming village in South India where exposure to inorganic arsenic was generally from synthetic phosphate fertilizers [OR: 5.56 (95% CI: 2.42 to 12.7)] (Velmurugan et al., 2018). In a cross-sectional study done in Mexican children, the concentration of total arsenic in urine was associated with a 0.058-mm (95% CI: 0.0198–0.095) increase in cIMT among children in Mexico with >70 ng total arsenic/mL in urine. Drinking water concentrations of arsenic were reported to range between 3 and 135 µg/L at the time of the evaluation (see Figure 3-10) (Osorio-Yáñez et al., 2013). The association of arsenic exposure with cIMT was increased when methylation capacity (Huang et al., 2009) and activity of a paraoxonase gene, PON1, were low (Li et al., 2009). Modification of this association by genotypes of GSTM1, APOE, and HO-1 (Wu et al., 2010b; Hsieh et al., 2008b; Wang et al., 2007; Chiou et al., 2001b) and homocysteine level (Wu et al., 2006) was observed across these cohorts providing evidence that these factors may confer susceptibility to arsenic-associated cardiovascular effects.

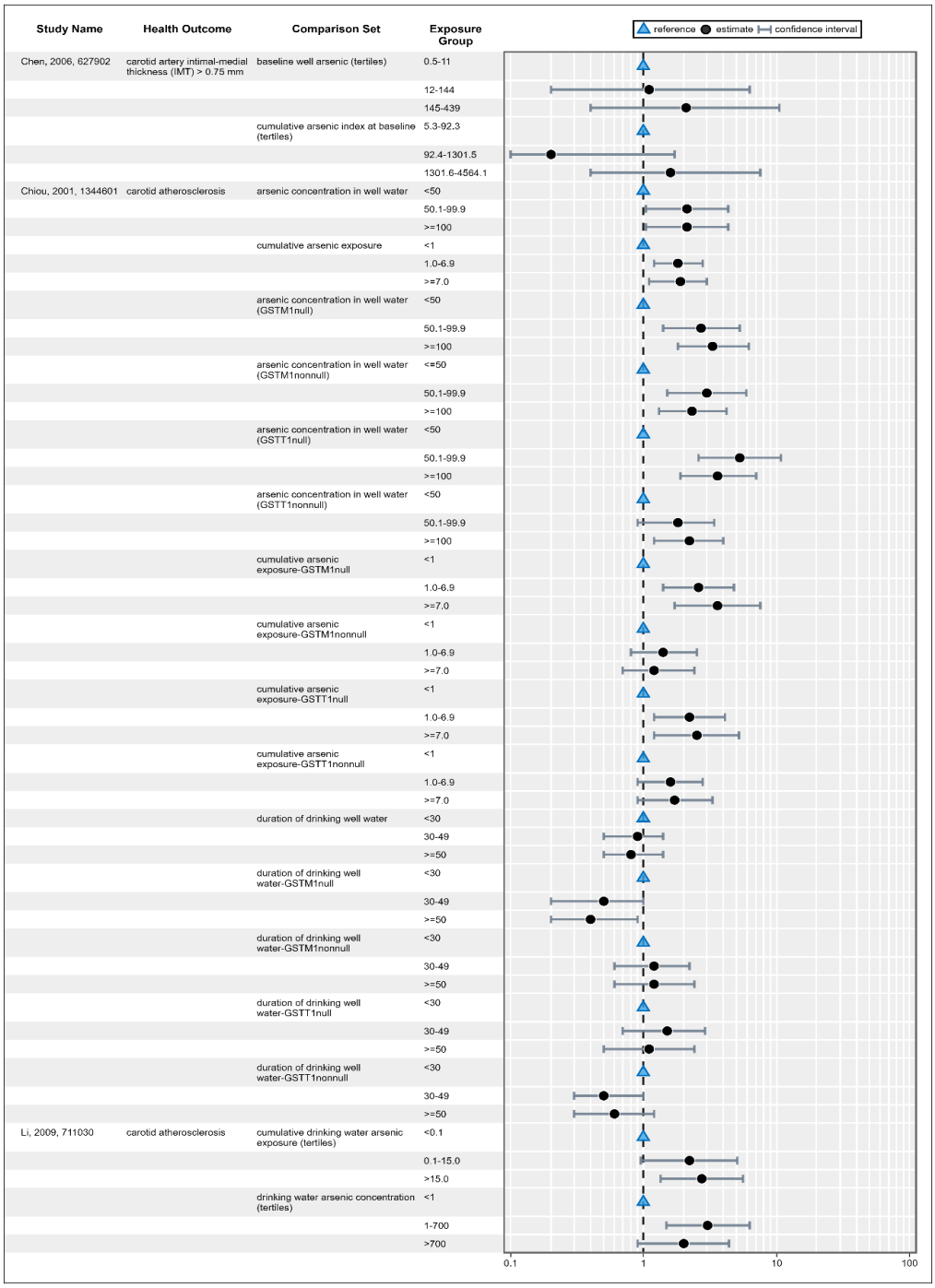


Study Name	Health Outcome	Comparison Set	Exposure Group	design	countries
Wu, 2006, 628580	carotid atherosclerosis	drinking water arsenic concentration (tertiles)	<=50.00	Case-control	Taiwan
			50.01-100.00	Case-control	Taiwan
			>=100.01	Case-control	Taiwan
		cumulative drinking water arsenic exposure (tertiles)	<=1.70	Case-control	Taiwan
			1.71-4.20	Case-control	Taiwan
			>=4.21	Case-control	Taiwan
Wang, 2002, 628509	carotid artery plaque or IMT >=1.0mm	cumulative drinking water arsenic exposure	0	Cohort (Prospective)	Taiwan
			0.1-19.9	Cohort (Prospective)	Taiwan
			>=20	Cohort (Prospective)	Taiwan
	IMT >=1.0mm	cumulative drinking water arsenic exposure	0	Cohort (Prospective)	Taiwan
			0.1-19.9	Cohort (Prospective)	Taiwan
			>=20	Cohort (Prospective)	Taiwan
	plaque of the carotid artery	cumulative drinking water arsenic exposure	0	Cohort (Prospective)	Taiwan
			0.1-19.9	Cohort (Prospective)	Taiwan
			>=20	Cohort (Prospective)	Taiwan
Hsieh, 2008, 627503	carotid atherosclerosis	drinking water arsenic concentration	<=10	Nested case-control	Taiwan
			10.1-50.0	Nested case-control	Taiwan
			>=50.1	Nested case-control	Taiwan
		cumulative drinking water arsenic exposure	<=0.2	Nested case-control	Taiwan
			0.3-1	Nested case-control	Taiwan
			>=1.1	Nested case-control	Taiwan
Wang, 2007, 628474	carotid atherosclerosis	arsenic concentration in well water (model I)	<=10	Nested case-control	Taiwan
			10.1-50.0	Nested case-control	Taiwan
			>=50.1	Nested case-control	Taiwan
		arsenic concentration in well water (model II)	<=10	Nested case-control	Taiwan
			10.1-50.0	Nested case-control	Taiwan
			>=50.1	Nested case-control	Taiwan
Wu, 2010, 710944	carotid atherosclerosis	average drinking water arsenic exposure (Lanyang cohort)	<=10	Nested case-control	Taiwan
			10.1-50	Nested case-control	Taiwan
			50.1-100	Nested case-control	Taiwan
			100.1-300	Nested case-control	Taiwan
			>300	Nested case-control	Taiwan
		average drinking water arsenic exposure (LMN cohort)	<=300	Nested case-control	Taiwan
			300-750	Nested case-control	Taiwan
			>750	Nested case-control	Taiwan

Figure 3-13. Thumbnail schematic of case-control and cohort studies of atherosclerosis in response to inorganic arsenic exposure, ratio measures, drinking water, categorical exposure (see interactive data graphic).



(a) Ratio measures, urine, categorical exposure



(b) Ratio measures, drinking water, categorical exposure

Figure 3-14. Thumbnail schematic of cross-sectional studies of atherosclerosis in response to inorganic arsenic exposure (a) ratio measures, urine, categorical exposure; (b) ratio measures, drinking water, categorical exposure (see interactive data graphic).

Summary

Overall, these epidemiological studies indicate that low-to-moderate arsenic concentrations are associated with increased cIMT, supporting the associations of arsenic with atherosclerosis observed in other epidemiological studies. Effects on cIMT were greatest among those with lower methylation capacity indicated by metabolites in urine and among those with genes associated with lower methylation capacity or the regulation of atherosclerosis.

Electrocardiogram abnormalities

The literature review identified nine epidemiological studies, four case-control/cohort (Wang et al., 2010; Moon et al., 2018; Liao et al., 2009; Chen et al., 2013d) and five cross-sectional (Yildiz et al., 2008; Wang et al., 2009; Mumford et al., 2007; Mordukhovich et al., 2009; Feng et al., 2014), considered *medium* or *high* confidence that evaluated the association between iAs exposure and electrocardiogram abnormalities (see Figure 3-15 and Figure 3-16). These endpoints include repolarization abnormalities, such as QT prolongation, which reflect involvement of the autonomic nervous system and typically co-occur with hypertension. Long QT interval, or QT prolongation, is a repolarization abnormality associated with an increased risk of sudden death (Solti et al., 1989). QT prolongation is consistent with sympathetic hyperreactivity and often co-occurs with LVH and hypertension (Solti et al., 1989).

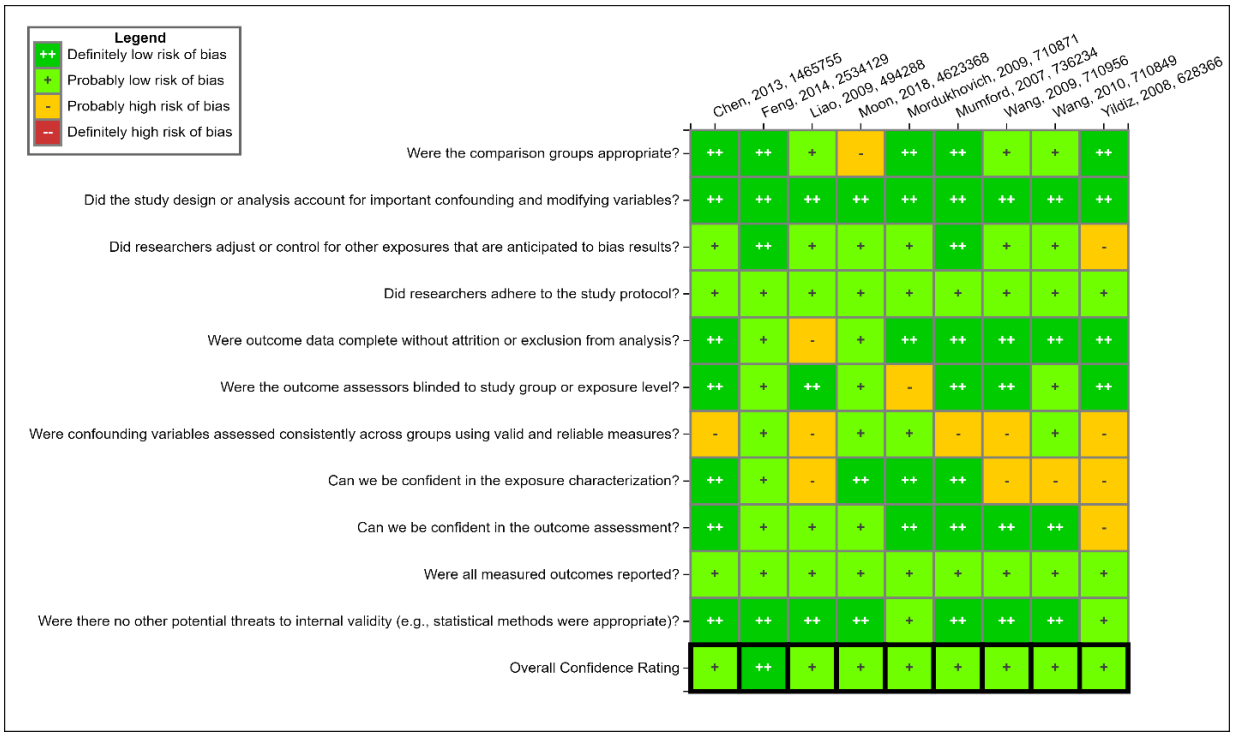


Figure 3-15. Study evaluation ratings for references evaluating electrocardiogram abnormalities (see interactive version in HAWC).

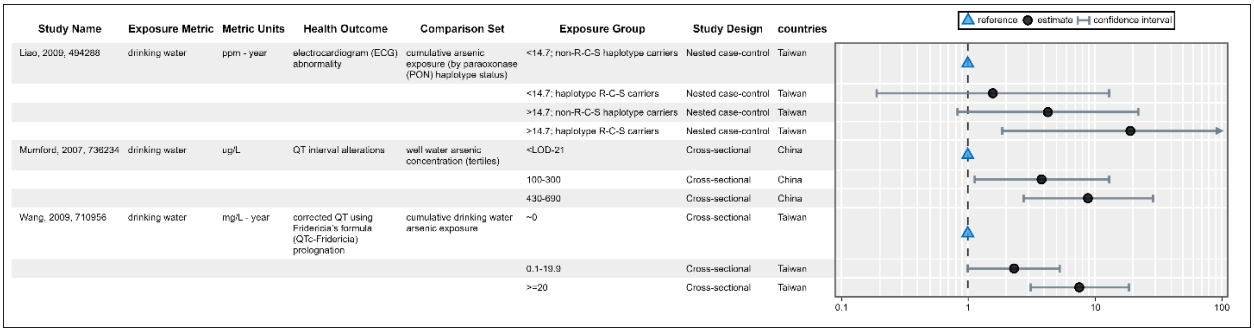


Figure 3-16. Thumbnail schematic of studies addressing the association electrocardiogram abnormalities and inorganic arsenic exposure, ratio measures, drinking water, categorical exposure (see interactive graphic).

Moon et al. (2018) found associations of the sum of iAs and methylated arsenic in urine with ECG outcomes including QT interval (QTc) and JT interval (another marker of cardiac conduction) among American Indians in the SHS (urine arsenic median (IQR): 8.6 (5.2, 14.4) µg/g creatinine) and the Strong Heart Family Study (SHFS) (urine arsenic median(IQR): 4.3 (2.9, 7.1) µg/g creatinine. Participants had no heart disease or reported use of medications that could affect repolarization. In a cross-sectional analysis of older adult men enrolled in the U.S.-based Normative Aging Study, Mordukhovich et al. (2009) found that increasing toenail arsenic concentration (median (IQR): 0.069 (0.052, 0.11) µg/g) was associated with an increase in QTc. Arsenic exposure is presumed to be "low" in this cohort of residents of greater Boston, MA. Associations between arsenic exposure and QTc were also observed in cohorts where the highest arsenic concentrations in drinking water are typically higher than highest levels found in U.S. cohorts. Chen et al. (2013d) observed associations of both drinking water arsenic concentration (range: 0.1–790 µg/L) and urinary arsenic concentration (range: 7–4,306 µg/g creatinine) with heart rate corrected QTc among women, but not among men, in the HEALS cohort. Chronic arsenic exposure was associated with QTc prolongation in a small study of residents of Inner Mongolia exposed to arsenic concentrations in well water ranging from nondetectable (0.2 µg/L) to 690 µg/L (Mumford et al., 2007); The association was stronger in women than in men in this study, similar to the findings of (Chen et al., 2013d).

In addition to the studies examining repolarization parameters described above, a cross-sectional study of the association of heart rate variability with concentrations of various metals in urine conducted in Wuhan China reports a 19.8% (95% CI: 2.60, 33.96%) reduction in low frequency (LF) with a 10-fold increase in urinary arsenic concentration (geometric mean: 2.40 µg/mmol creatinine). Associations of urinary arsenic with other heart rate variability parameters were not significant and consequently not reported (Feng et al., 2014). Comparisons of those living in areas of Bangladesh where arsenic poisoning is endemic, to those living in other areas of these countries with relatively low concentrations of arsenic in drinking water also report correlations with QT prolongation and other repolarization parameters (Yildiz et al., 2008; Ahmad et al., 2006).

Highly exposed population: Southwestern Taiwan

Studies from the highly exposed cohort of southwestern Taiwan provide support for the effect of relatively high arsenic exposure on QT prolongation. These studies are addressed separately due to their limited relevance to U.S. populations, where the average drinking water concentrations are 500-fold lower, and the highest concentrations observed are still 10- to 100-fold lower. Wang et al. (2009) observed an association between cumulative arsenic exposure and QT prolongation. Higher cumulative exposures were associated with more pronounced QT prolongation decades after exposure had ended. In addition, clinical outcomes including IHD and carotid atherosclerosis (Wang et al., 2009) were associated with QTc prolongation in this cohort. In a follow-up study, Wang et al. (2010) examined the association of QT dispersion (QTD), considered an early biomarker of atherosclerosis, and cumulative arsenic exposure. An exposure-dependent association of cumulative arsenic exposure with QTD was observed. In addition, associations of QTD with IHD, carotid atherosclerosis, and cardiovascular-related mortality, were reported. In another, smaller study of this cohort, Liao et al. (2009) observed an association between arsenic exposure and electrocardiogram abnormalities; polymorphisms in two paraoxonase genes significantly increased the risks of ECG abnormality.

Summary

Overall, these studies provide consistent evidence of an association between QT prolongation and iAs exposure, thus supporting associations observed with CHD and hypertension in relation to arsenic. A dose-response gradient was observed in some studies [e.g., (Wang et al., 2009; Mumford et al., 2007; Liao et al., 2009)]. There is limited evidence that the association with QT prolongation may be stronger in women.

Cerebrovascular Disease and Stroke

The literature review identified 13 epidemiological studies, 9 case-control/cohort (Wade et al., 2009; Tsinovoi et al., 2018; Rahman et al., 2014; Moon et al., 2013; Merrill et al., 2017; Lewis et al., 1999; Farzan et al., 2015a; D'Ippoliti et al., 2015; Chen et al., 2011b) and cross-sectional/ecological (Zierold et al., 2004; Xia et al., 2009; Lisabeth et al., 2010; Chiou et al., 1997) considered *medium* or *high* confidence that evaluated the association between iAs exposure and cerebrovascular disease and stroke (see Figure 3-17). In the HEALS cohort in Bangladesh, Chen et al. (2011b) reported weak to null associations of baseline concentrations of iAs in drinking water [HR: 1.07 (95% CI: 0.54, 2.12)]and urine [HR: 1.03 (0.53, 2.03)] with cerebrovascular disease-related mortality in models (see Figure 3-18). In another prospective cohort study conducted in Bangladesh, Rahman et al. (2014) found an exposure response for drinking water arsenic and stroke mortality across a range of exposures (0.5 to 3,644 µg/L), including those considered relevant to the U.S. Comparing those exposed to concentrations ≥50 µg/L to the reference group (<10 µg/L), the HR was 1.35 (95% CI: 1.04–1.75) (see Figure 3-18). Comparing those exposed to

drinking water concentrations of 10–49 μg/L to the reference group, the HR was 1.20 (95% CI: 0.92–1.57). Stronger associations were reported for women than for men in this study.

Several additional studies add to the evidence base, including two analyses of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, which is a study of adults (≥45 years old) who live in the continental U.S. (Merrill et al., 2017). Participants were assigned levels of arsenic derived from concentrations in environmental media (i.e., stream sediments and soils) recorded in the National Geologic Survey (NGS) database. An association between environmental arsenic concentration and incident stroke was observed [HR: 1.20 (95% CI: 0.98, 1.46) comparing the highest to the lowest quartile (6.42, 49.55 ppm) to (0.75, 2.15 ppm), respectively]. In the other REGARDS analysis Tsinovoi et al. (2018) examined the association of total urinary arsenic among a subcohort of n = 671 cases and n = 2,486 controls. Inorganic arsenic and arsenic metabolites were measured in a random sample of the subcohort (n = 199), with incident stroke (see Figure 3-18). No associations with total arsenic in the subcohort [HR: 1.01 (0.74–1.36) comparing the highest (≥20.55 μg/g creatinine) to the lowest quintile (<4.22 μg/g creatinine)] or with total inorganic arsenic among the random sample [HR 0.91 (0.64–1.30) per unit increase] were observed. A positive association with MMA was observed in the random sample of subjects with urinary metabolite measurements [HR: 1.98 (95% CI: 1.12– 3.50). No hazard ratio increase was observed by Farzan et al. (2015a) in their prospective analysis of the association between toenail arsenic and stroke-related mortality among participants in the New Hampshire Skin Cancer Study. However, when the Farzan et al. (2015a) cohort was evaluated across μg/g toenail exposure ranges (0.01–0.07, 0.07–0.11 and 0.11–3.26), relative risks for IHD- and stroke-related mortality were elevated in higher exposed groups over the lower reference group.

In the large study of Italian municipalities described previously, D'Ippoliti et al. (2015) reported positive associations of cumulative arsenic dose indicator, which accounted for lifetime intensity and duration of arsenic exposure given drinking water habits, with stroke in men (HR 1.74, 95% CI: 1.22–2.48) and women (1.82, 95% CI: 1.32–2.51). The results presented in parentheses compare the highest tertile index category (>804.0 μg/L) to the reference category (≤204.9 μg/L). Positive associations also were observed comparing the middle tertile to the reference category and also when exposure contrasts were determined based on average water concentration (10–20 μg/L and >20 μg/L) (see Figure 3-18).

Several additional studies assessed the association of iAs exposure with stroke or cerebrovascular outcomes (see Figure 3-19). Chiou et al. (1997) reported a positive association between iAs concentration in drinking water and the prevalence of cerebrovascular disease and cerebral infarction in northeastern Taiwan (range of arsenic in well water: <0.1– ≥300 μg/L). Inverse or null associations of arsenic with stroke prevalence or stroke-related mortality, however, have also been reported in studies of Inner Mongolia, China (Wade et al., 2009; Xia et al., 2009) and Utah, U.S. (Lewis et al., 1999).

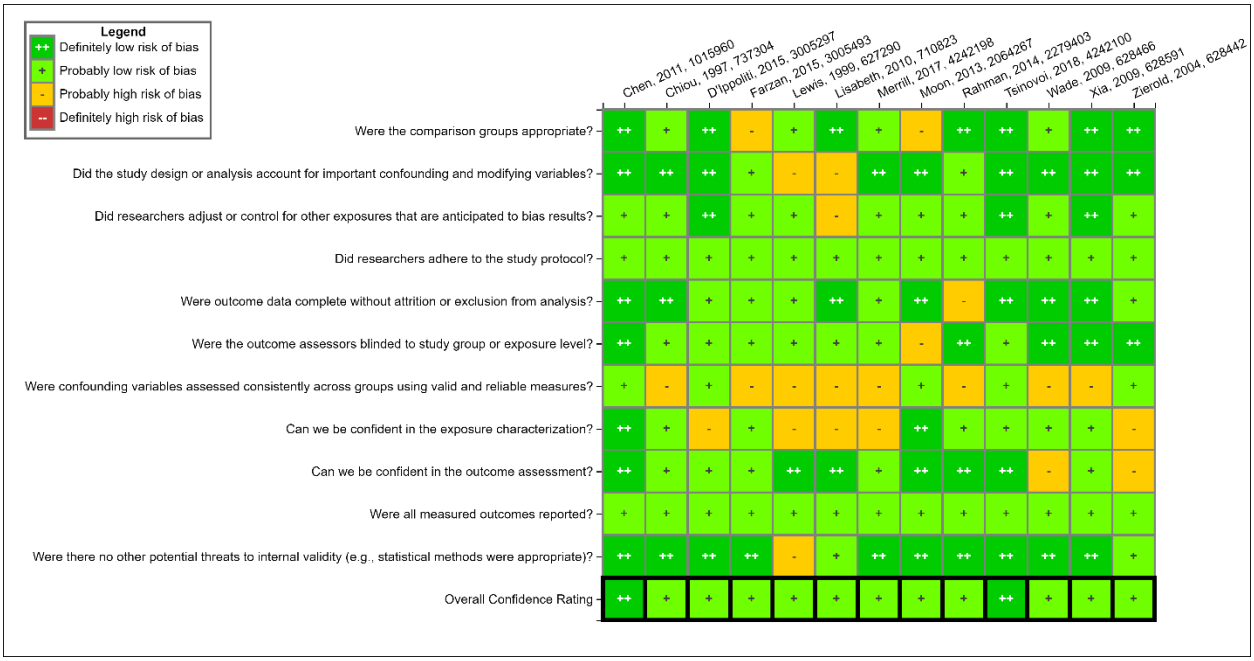
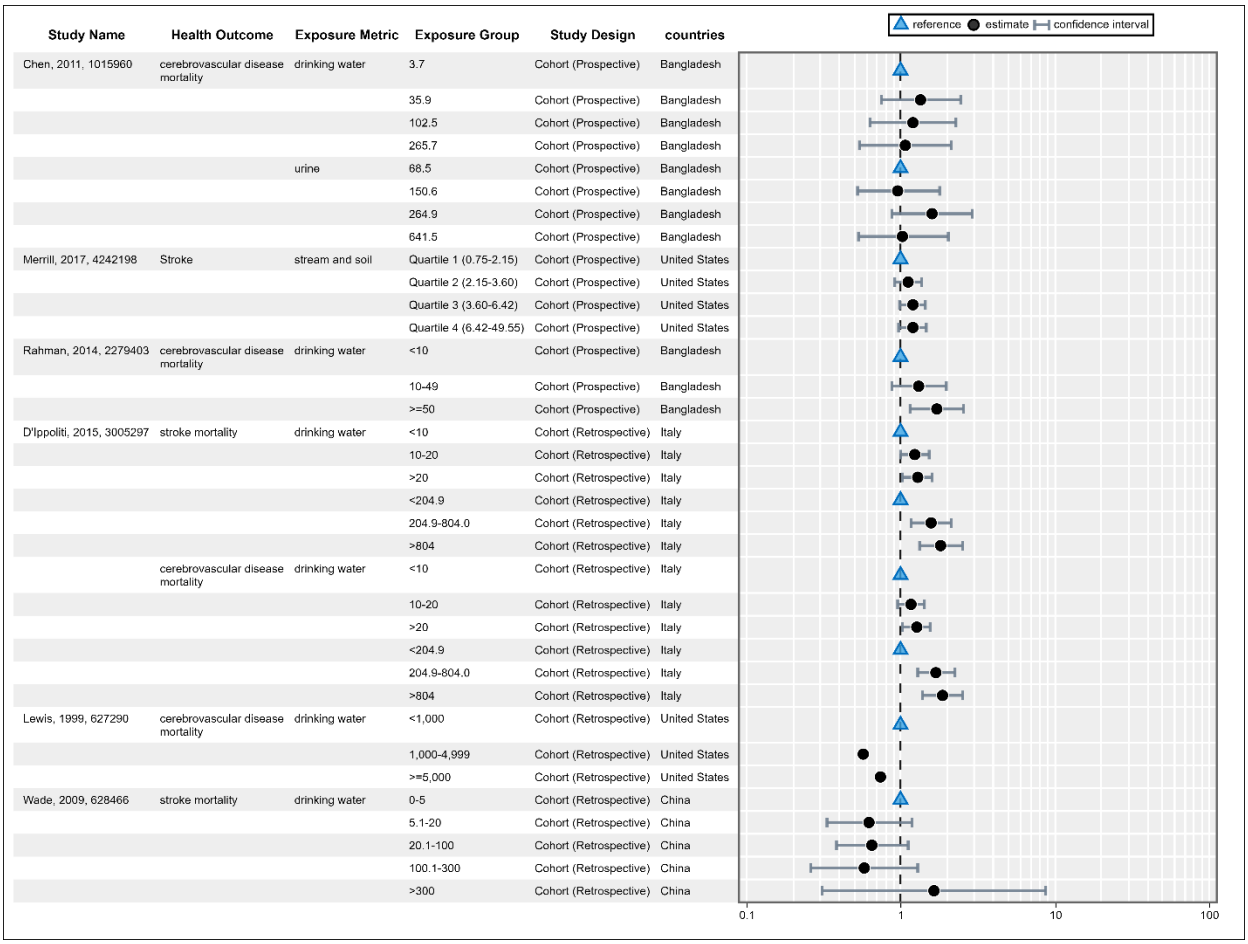
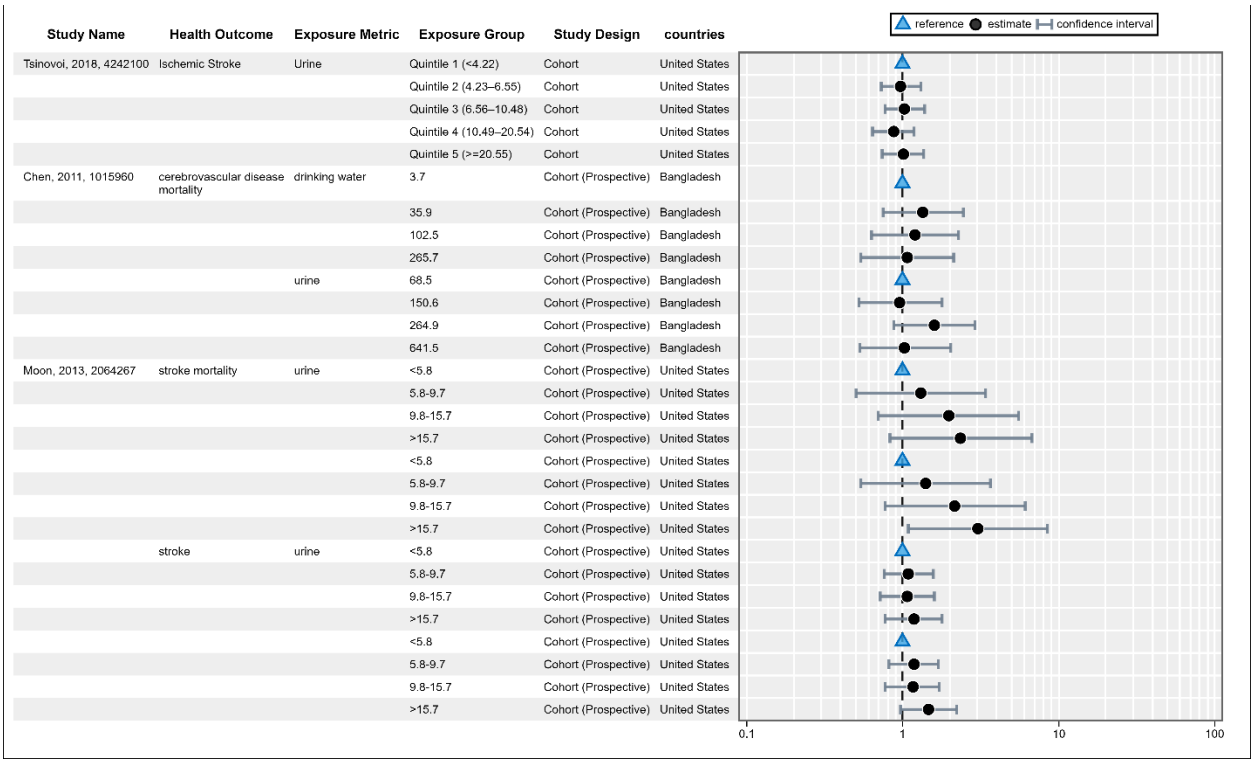


Figure 3-17. Study evaluation ratings for references evaluating cerebrovascular disease and stroke (see interactive version in HAWC).



Study Name	Health Outcome	Exposure Metric	Exposure Group	Study Design	countries
Chen, 2011, 1015960	cerebrovascular disease mortality	drinking water	3.7	Cohort (Prospective)	Bangladesh
			35.9	Cohort (Prospective)	Bangladesh
			102.5	Cohort (Prospective)	Bangladesh
			265.7	Cohort (Prospective)	Bangladesh
		urine	68.5	Cohort (Prospective)	Bangladesh
			150.6	Cohort (Prospective)	Bangladesh
			264.9	Cohort (Prospective)	Bangladesh
			641.5	Cohort (Prospective)	Bangladesh
Merrill, 2017, 4242198	Stroke	stream and soil	Quartile 1 (0.75-2.15)	Cohort (Prospective)	United States
			Quartile 2 (2.15-3.60)	Cohort (Prospective)	United States
			Quartile 3 (3.60-6.42)	Cohort (Prospective)	United States
			Quartile 4 (6.42-49.55)	Cohort (Prospective)	United States
Rahman, 2014, 2279403	cerebrovascular disease mortality	drinking water	<10	Cohort (Prospective)	Bangladesh
			10-49	Cohort (Prospective)	Bangladesh
			>=50	Cohort (Prospective)	Bangladesh
D'Ippoliti, 2015, 3005297	stroke mortality	drinking water	<10	Cohort (Retrospective)	Italy
			10-20	Cohort (Retrospective)	Italy
			>20	Cohort (Retrospective)	Italy
			<204.9	Cohort (Retrospective)	Italy
			204.9-804.0	Cohort (Retrospective)	Italy
			>804	Cohort (Retrospective)	Italy
	cerebrovascular disease mortality	drinking water	<10	Cohort (Retrospective)	Italy
			10-20	Cohort (Retrospective)	Italy
			>20	Cohort (Retrospective)	Italy
			<204.9	Cohort (Retrospective)	Italy
			204.9-804.0	Cohort (Retrospective)	Italy
			>804	Cohort (Retrospective)	Italy
Lewis, 1999, 627290	cerebrovascular disease mortality	drinking water	<1,000	Cohort (Retrospective)	United States
			1,000-4,999	Cohort (Retrospective)	United States
			>=5,000	Cohort (Retrospective)	United States
Wade, 2009, 628466	stroke mortality	drinking water	0-5	Cohort (Retrospective)	China
			5.1-20	Cohort (Retrospective)	China
			20.1-100	Cohort (Retrospective)	China
			100.1-300	Cohort (Retrospective)	China
			>300	Cohort (Retrospective)	China

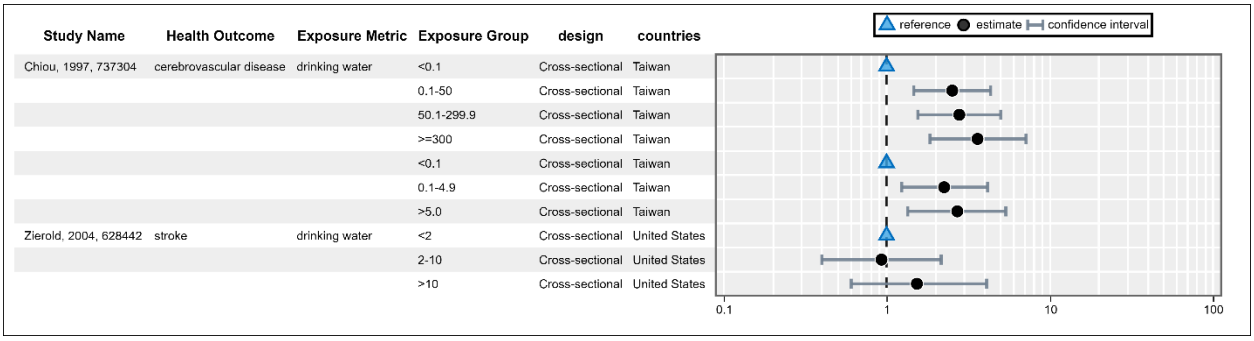
(a) Ratio measures, drinking water, categorical exposure



Study Name	Health Outcome	Exposure Metric	Exposure Group	Study Design	countries
Tsinovoi, 2018, 4242100	Ischemic Stroke	Urine	Quintile 1 (<4.22)	Cohort	United States
			Quintile 2 (4.23–6.55)	Cohort	United States
			Quintile 3 (6.56–10.48)	Cohort	United States
			Quintile 4 (10.49–20.54)	Cohort	United States
			Quintile 5 (>=20.55)	Cohort	United States
Chen, 2011, 1015960	cerebrovascular disease mortality	drinking water	3.7	Cohort (Prospective)	Bangladesh
			35.9	Cohort (Prospective)	Bangladesh
			102.5	Cohort (Prospective)	Bangladesh
			265.7	Cohort (Prospective)	Bangladesh
		urine	68.5	Cohort (Prospective)	Bangladesh
			150.6	Cohort (Prospective)	Bangladesh
			264.9	Cohort (Prospective)	Bangladesh
			641.5	Cohort (Prospective)	Bangladesh
Moon, 2013, 2064267	stroke mortality	urine	<5.8	Cohort (Prospective)	United States
			5.8-9.7	Cohort (Prospective)	United States
			9.8-15.7	Cohort (Prospective)	United States
			>15.7	Cohort (Prospective)	United States
			<5.8	Cohort (Prospective)	United States
			5.8-9.7	Cohort (Prospective)	United States
			9.8-15.7	Cohort (Prospective)	United States
			>15.7	Cohort (Prospective)	United States
	stroke	urine	<5.8	Cohort (Prospective)	United States
			5.8-9.7	Cohort (Prospective)	United States
			9.8-15.7	Cohort (Prospective)	United States
			>15.7	Cohort (Prospective)	United States
			<5.8	Cohort (Prospective)	United States
			5.8-9.7	Cohort (Prospective)	United States
			9.8-15.7	Cohort (Prospective)	United States
			>15.7	Cohort (Prospective)	United States

(b) Ratio measures, biomarkers, categorical exposure

Figure 3-18. Thumbnail schematic of case-control and cohort studies of cerebrovascular disease and stroke in response to inorganic arsenic exposure, (a) ratio measures, drinking water, categorical exposure; (b) ratio measures, biomarkers, categorical exposure (see interactive data graphic).



Study Name	Health Outcome	Exposure Metric	Exposure Group	design	countries
Chiou, 1997, 737304	cerebrovascular disease	drinking water	<0.1	Cross-sectional	Taiwan
			0.1-50	Cross-sectional	Taiwan
			50.1-299.9	Cross-sectional	Taiwan
			>=300	Cross-sectional	Taiwan
			<0.1	Cross-sectional	Taiwan
			0.1-4.9	Cross-sectional	Taiwan
			>5.0	Cross-sectional	Taiwan
Zierold, 2004, 628442	stroke	drinking water	<2	Cross-sectional	United States
			2-10	Cross-sectional	United States
			>10	Cross-sectional	United States

Figure 3-19. Thumbnail schematic of cross-sectional studies of cerebrovascular disease and stroke in response to inorganic arsenic exposure, ratio measures, drinking water, categorical exposure (see interactive data graphic).

Supplemental information: Meta-analysis

In the meta-analysis by Moon et al. (2012), relatively weak (compared with CHD) and imprecise pooled estimates for stroke were reported. To obtain the pooled estimates for high-exposure areas and areas with low-to-moderate exposure, the authors stratified the studies by mean iAs concentration greater than 50 μg/L or less than 50 μg/L and compared the risk in the highest exposure group in each study to the risk in the lowest exposure group. The pooled estimates obtained were 1.08 (95% CI: 0.98–1.19) in high-exposure areas, and 1.07 (95% CI: 0.96, 1.20) in low to moderate exposure areas.

Summary

Findings from the epidemiological studies are limited with some uncertainty. Overall, epidemiological studies provide primarily consistent evidence of an association between arsenic exposure and cerebrovascular disease and stroke and mortality from cerebrovascular causes. A dose-response gradient was observed in many (Rahman et al., 2014; Moon et al., 2013; Merrill et al., 2017; D'Ippoliti et al., 2015; Chiou et al., 1997; Chen et al., 2011b) but not all studies. The gradient was consistently observed in populations with higher (>100 μg/L) concentrations of iAs in drinking water, but some inconsistencies were observed across study findings.

Other Vascular Diseases

The literature review identified seven epidemiological studies, five case-control/cohort (Tseng et al., 2005; Pi et al., 2005; Hsieh et al., 2008a; D'Ippoliti et al., 2015; Chiou et al., 2005) and two cross-sectional (Tseng et al., 1996; Tseng et al., 1997), considered medium or high confidence that evaluated the association between iAs exposure and other vascular disease (see Figure 3-20). Blackfoot disease, a peripheral vascular disease (PVD) characterized by gangrene in the extremities, is well documented in the southwestern coastal region of Taiwan, where the population was exposed to high concentrations of iAs (700–930 μg/L) in drinking water for several decades (Tseng, 2002). Arsenic exposure also is associated with microvascular diseases, including those affecting the nervous and renal systems in this population. Erectile dysfunction (Hsieh et al., 2008a) and PVD (Tseng et al., 1996; Tseng et al., 2005) are reported in this southwestern Taiwan region. Tseng et al. (2005) found that those with a lower capacity to methylate arsenic had a higher risk of PVD. In a prospective analysis of several Italian municipalities, HRs for mortality from PVD were increased but confidence intervals were wide for both males and females (study participants were followed from 1990 to 2010 and exposed, on average, to 19.3 μg/L for 39.5 years) (D'Ippoliti et al., 2015). In a study conducted in China, Pi et al. (2005) reported a reduction in response to cold stress, a symptom of PVD, after an intervention to reduce exposure to arsenic in drinking water among patients with chronic arsenic poisoning. Chiou et al. (2005) used arsenic levels in well water as indices of previous ingestion levels, finding an association between drinking water arsenic concentration and microvascular disease prevalence in the cohort. These few studies of vascular

endpoints provide consistent evidence for an array of effects of arsenic on the vascular system at high concentrations.

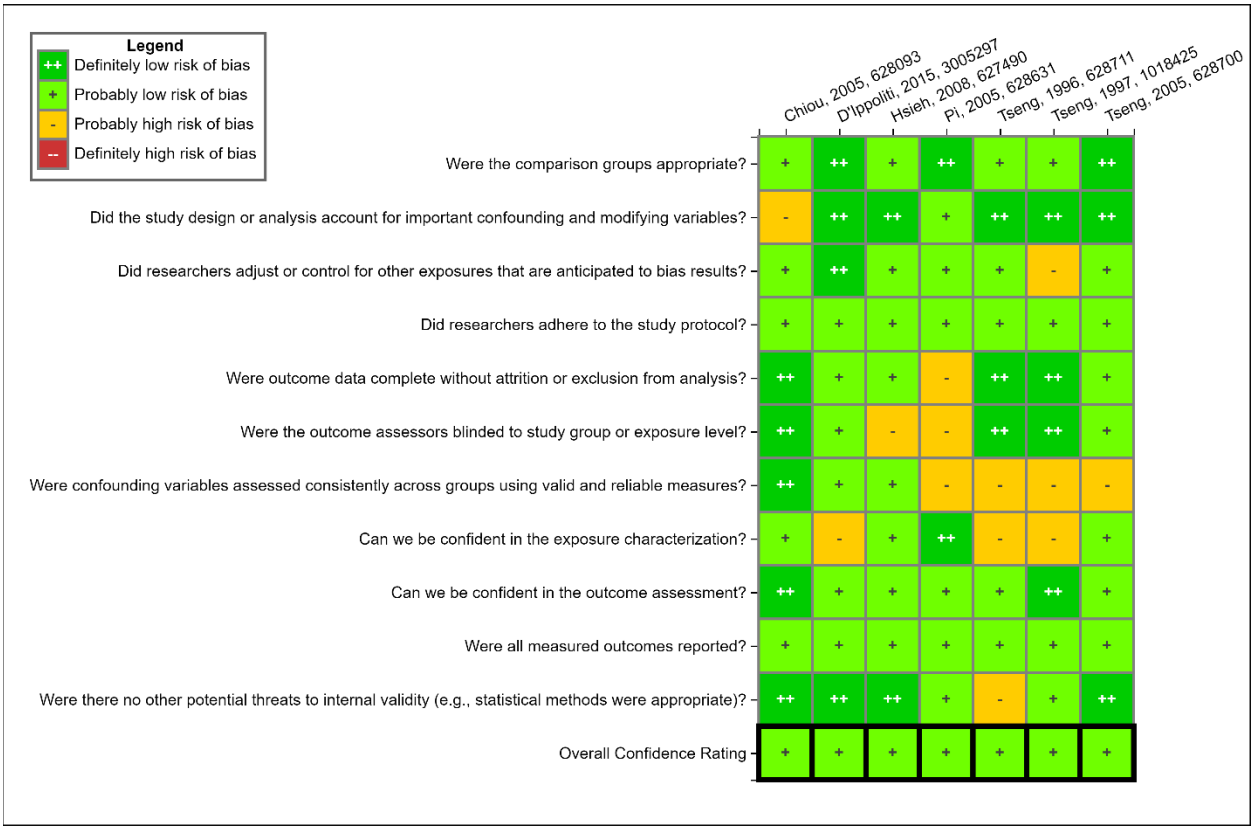


Figure 3-20. Study evaluation ratings for references evaluating other vascular diseases (see interactive version in HAWC).

Circulatory Markers of Cardiovascular Risk

Circulating blood or serum markers of CVD risk were examined in 10 epidemiological studies, three cohort (Moon et al., 2017a; Kuo et al., 2018; Das et al., 2012) and seven cross-sectional (Wu et al., 2012b; Osorio-Yáñez et al., 2013; Mendez et al., 2016; Karim et al., 2013; Chen et al., 2007; Chen et al., 2012b; Burgess et al., 2013) (see Figure 3-21). Moon et al. (2017a) examined the association of iAs in urine (median (IQR): 8.4 (5.1, 14.3) µg/g creatinine) with plasma fibrinogen, PAI-1, and CRP among American Indians participants of the Strong Heart Study (SHS). A positive association with plasma fibrinogen was found among those with diabetes. These biomarkers were not associated with iAs exposure among those without diabetes. Low levels of iAs in drinking water (mean 7.65 µg/L) were associated with serum matrix metalloproteinase-9 in residents of Arizona and Mexico (Burgess et al., 2013). The association of asymmetric dimethylarginine with cIMT in arsenic-exposed children (drinking water arsenic concentration range: 3–135 µg/L) in Mexico provides another potential biomarker of interest (Osorio-Yáñez et al., 2013).

A study of the HEALS cohort in Bangladesh reported cross-sectional associations of baseline well water arsenic concentration (range: 0.10–500.62 µg/L) with markers of endothelial dysfunction and vascular inflammation (Wu et al., 2012b). Chen et al. (2007) found a significant association with endothelial adhesion molecules, which have been associated with endothelial dysfunction, in this cohort (range: 0.1–864.0 µg/L). Karim et al. (2013) reported correlations between arsenic concentrations in water, hair, and nails with markers of inflammation and coagulation, including C-reactive peptide and oxidized low-density lipoprotein as well as with markers of endothelial dysfunction among participants in another study in rural Bangladesh. Das et al. (2012) reported a significant increase in inflammatory cytokine levels associated with cardiovascular disease (IL6 and IL8) in arsenic-exposed (mean (SD): 202.68 (188.12) µg/L) vs. unexposed (mean (SD): 5.38 (2.06) µg/L) individuals in West Bengal, India. Taken together the evidence indicates that there is a correlation between inorganic arsenic exposure and increased markers for circulatory risk.

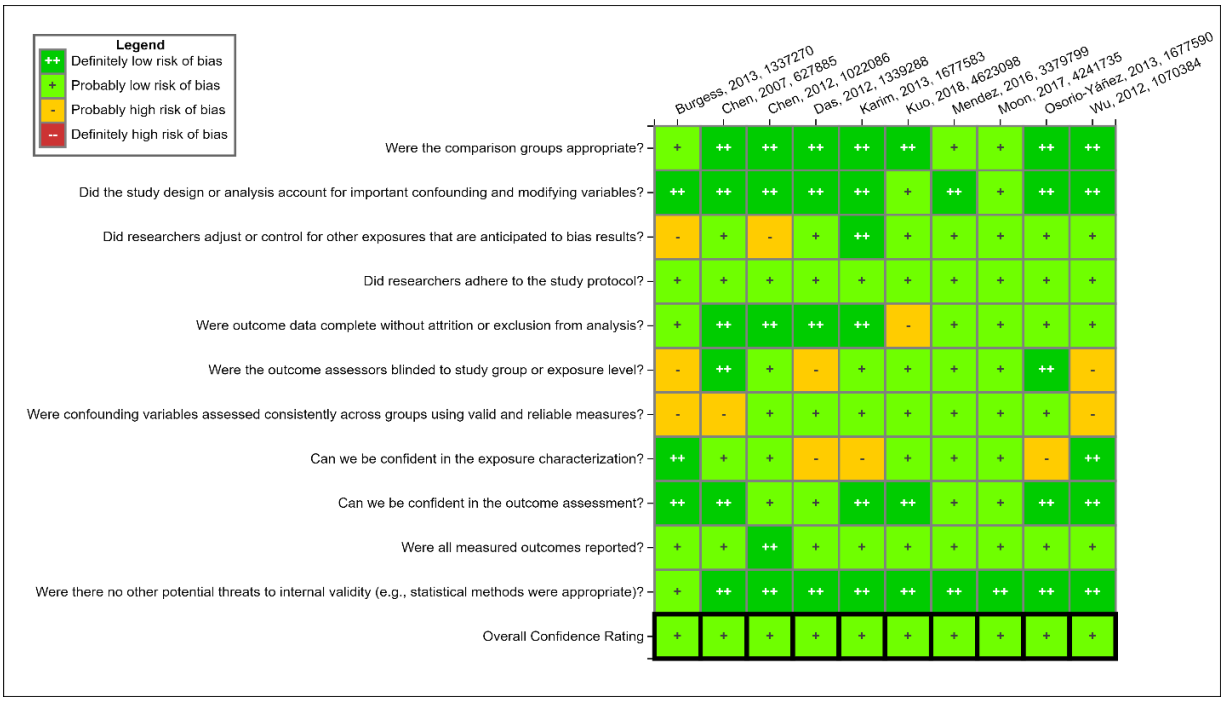


Figure 3-21. Study evaluation outcomes for references evaluating circulatory markers for CVD risk (see interactive version in HAWC).

Highly exposed population: Southwest Taiwan

Lipid abnormalities are an established risk factor for CVD. Lipid profiles did not differ between cases and non-cases of PVD in the highly exposed population of southwestern Taiwan (Tseng et al., 1997), but this observation might reflect the inadequacy of measuring lipid profiles several years after arsenic exposure. An association was reported between cumulative arsenic

exposure (ppm-years) and abnormal lactate dehydrogenase activity, a marker of CVD risk, in this cohort (Liao et al., 2012).

Mechanistic Observations and Biological Plausibility

As summarized above there is strong evidence from prospective cohort and case control studies showing an association between iAs exposure and ischemic heart disease (IHD) related outcomes, including IHD incidence and mortality. There is also consistent evidence from case control, cohort, and cross-sectional studies reporting generally consistent exposure dependent associations between arsenic and atherosclerosis. The mechanistic literature database includes numerous in vivo and in vitro studies evaluating these factors with a majority of the experimental data focusing on oxidative stress, angiogenesis, atherosclerotic plaque formation, and effects on vascular tissue (for more information see Appendix A of the iAs protocol). Below we discuss the mechanistic evidence for each of these mechanisms and their implications on IHD and atherosclerosis. Atherosclerosis is a disease of the arterial wall which involves thickening and loss of elasticity of the walls of the arteries that occurs with formation of atherosclerotic plaques within the arterial intima, the inner layer of the arteries lined by a mono layer of endothelial cells which are in direct contact with blood. Atherosclerotic plaques are composed of cholesterol, fatty substances, cellular waste products, calcium, and fibrin. Build-up of these plaques can occlude blood flow of oxygen rich blood and lead to myocardial infarctions, stroke, and death It is widely accepted that atherosclerosis is a process that involves a chronic inflammatory state, which leads to endothelial cell activation, dysfunction and accumulation of lipids, recruitment of leukocytes, proliferation of smooth muscle cells within the arterial wall, development of foam cells and eventually, deposition of extracellular matrix (Ross, 1999; Libby et al., 2011). It should be noted that the development and progression of atherosclerosis is a dynamic and multistep process that occurs over the course of multiple years. However, the progression of the disease can still be grouped into three distinct stages: (i) early changes (ii) plaque formation and ultimately (iii) plaque disruption (Ross, 1999; Libby et al., 2011).

Stage 1: Early changes

As noted previously the development of atherosclerosis is a complex multistage process, a combination of two principal hypotheses that are widely accepted in the field. These include the stress of intimal cellular proliferation and the recurrence of thrombi which over time organize into clinically significant plaques (Sidhu et al., 2015; Ross, 1999). The increase in reactive oxygen species (ROS) has been widely documented as an initiating event in the progression of the disease. Increases in ROS are normally tempered by antioxidant enzymes such as gluthatione S transferase and superoxide dismutase. When these antioxidant defenses are exhausted there is an increase in oxidative stress that can contribute to the depletion of tetrahydrobiopten (BH4), an essential cofactor in the synthesis of nitric oxide synthase. Depletion of BH4 further contributes to oxidative stress. Additionally, oxidative stress leads to the activation of inflammatory cytokines, such as

VCAM and ICAM, and systemic inflammation. Systemic inflammation leads to endothelial cell activation. Endothelial cell activation is typically a normal response to tissue injury or infection by endothelial cells in post-capillary venules to release chemokines that attract white blood cells (WBCs) to the area and concomitantly produce cell surface adhesion molecules that enables anchoring of leukocytes to the endothelial surface and transmigration to the site of injury. A pathologic version of this process during atherosclerotic plaque formation. Prolonged oxidative stress and or inflammatory states can alter the ability of endothelial cells to maintain homeostasis, this is known as endothelial cell dysfunction. Endothelial cell dysfunction leads to the development of pathological inflammatory processes, such as vascular disease and has been associated with metabolic disorders such as insulin resistance and type 2 diabetes (Esper et al., 2006).

Stage 2: Plaque formation.

Fatty streaks, atheromas and foam cell aggregates begin development after endothelial cell dysfunction occurs. Formation and progression of atherosclerotic plaques are largely driven by the migration of smooth muscle cells (SMCs) into the tunica intima as well as by the subsequent proliferation of SMCs post-migration (Sidhu et al., 2015; Libby et al., 2011). Overtime contribution from proinflammatory cytokines and growth factors such as PDGF, FGF, and TNF-alpha contribute to the formation of fatty streaks that further stimulate SMC migration and proliferation. This generates a cycle that maintains and further stimulates detrimental inflammation at the site of the developing plaque. Ultimately SMC migration leads to collagen synthesis and the genesis of an extracellular matrix component that functions to stabilize and forms a fibrous plaque.

Stage 3 Plaque disruption

The stability of the fibrous cap depends largely on the balance between ECM deposition and degradation. A fibrous cap may protrude into the arterial lumen and occlude arterial blood flow. Alternatively, plaques that contain less collagen are more likely to rupture and lead to adverse clinical outcomes such as myocardial infarction and stroke.

Inorganic arsenic exposure has been associated with increased risk of cardiovascular disease in both humans (Wade et al., 2015; Sohel et al., 2009; Moon et al., 2013; Chen et al., 2011b) and experimental animals (Srivastava et al., 2007; States et al., 2009; Lemaire et al., 2011). It was shown by Wu et al. (2010b) that there was an increase in atherosclerotic risk in Taiwanese individuals containing polymorphisms in GST gene. Additionally, it has been shown that the metabolism of arsenic, widely thought to have been a detoxifying mechanism, produces homocysteines as arsenic is methylated from arsenic to MMA to DMA. Elevated plasma homocysteine levels have been shown to be a reliable bioindicator of increased atherosclerotic risk and have been shown to contribute to ER stress, endothelial cell activation, inflammation, and cell proliferation (Papatheodorou and Weiss, 2007). Additionally, inorganic arsenic has been shown to lead to reactive oxygen species production and oxidative stress (see Appendix A of the iAs

protocol). As discussed previously prolonged oxidative stress leads to endothelial cell dysfunction, foam cell formation and overtime the progression of atherosclerosis.

Oxidative Stress

The increase in reactive oxygen species (ROS) has been widely documented as an initiating event in the progression of arsenic induced diseases, including atherosclerosis [see Appendix A of the iAs protocol and (Lind et al., 2021)]. Arsenic induces the formation of reactive oxygen species (ROS) such as $O_2^{\bullet-}$, H_2O_2, and $OH^{\bullet}$, through direct and indirect mechanisms throughout the system. Increases in ROS are normally tempered by antioxidant enzymes such as glutathione peroxidase, glutathione S transferase and superoxide dismutase (Handy and Loscalzo, 2022). However, when these antioxidant defenses are exhausted there is an increase in oxidative stress that can contribute to the depletion of tetrahydrobiopterin (BH4), an essential cofactor in the synthesis of nitric oxide synthase (NOS) (Wu et al., 2021). NOS is an enzyme that produces nitric oxide (NO), a signaling molecule that plays many roles in the cardiovascular system (Wu et al., 2021; Roy et al., 2023; Förstermann and Sessa, 2012; Carnicer et al., 2013) including regulation of myocardial function (Carnicer et al., 2013), inhibition of platelet aggregation and adhesion (Förstermann and Sessa, 2012), regulation of vascular smooth muscle proliferation (Roy et al., 2023; Förstermann and Sessa, 2012; Carnicer et al., 2013) and stimulation of angiogenesis (Roy et al., 2023; Förstermann and Sessa, 2012; Carnicer et al., 2013). Depletion of BH4 further contributes to oxidative stress. Increases in ROS production in endothelial cells, results in endothelial inflammation (Bunderson et al., 2004; Barchowsky et al., 1996; Barchowsky et al., 1999) and increases in the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1(VCAM 1). ICAM-1 and VCAM-1 are adhesion molecules expressed on the surface of endothelial cells that play a crucial role in the development of atherosclerotic plaques by facilitating the adhesion and migration of leukocytes to the arterial wall and subsequent plaque formation (Singh et al., 2023). Arsenic exposure (in vitro in rodent primary aorta endothelial and smooth muscle cells or in human lymphocytes) and subsequent ROS production induces ICAM-1 and VCAM-1 (Singh et al., 2023) as well as several genes associated with cellular inflammation, including interleukin-8, interleukin-1 beta, interleukin-6, and chemokine C-C motif ligand 2/monocyte chemotactic protein-1 (Simeonova et al., 2003; Wu et al., 2003).

ROS are also key mediators of vascular leakage, and loss of ROS homeostasis can contribute to vascular disease (Veeraraghavan et al., 2020; Chen et al., 2017). High levels of ROS in the system can cause vascular damage and vascular leakage. As an example, high levels of ROS can activate cell signaling pathways that lead to phosphorylation of VE-cadherin, a protein that plays a critical role in the maintenance of blood and lymphatic vessels, resulting in compromised adherens junctions (Veeraraghavan et al., 2020; Chen et al., 2017). High levels of ROS can also activate endothelial cells, which can lead to vascular leakage (Veeraraghavan et al., 2020; Chen et al., 2017). Lastly ROS can also lead to vascular remodeling by promoting vascular cell growth, inflammation, and deposition

of extracellular matrix (Lind et al., 2021; Chen et al., 2017). Arsenic-induced vascular leakage has been proposed to be instrumental in induction of CVD. Chen et al. (2008) reported increased vascular permeability in the skin of rats after intradermal injections of arsenic. The increased permeability resulted from increased production of ROS, specifically: nitric oxide, hydroxyl radical, and peroxynitrite. In an in vitro study in mouse brain endothelial cells, Bao et al. (2010) reported increased vascular permeability after treatment with 5-μM arsenic. The vascular permeability was mediated by ROS resulting from arsenic exposure, causing the release of vascular endothelial growth factor (VEGF). Arsenic stimulates the expression of VEGF partially by inducing the heme oxygenase-1 (HO1) system, through the inactivation of the transcription factor Bach 1, which allows Nrf2 (nuclear factor erythroid-derived 2 related factor-2) to bind to the HO-1 promoter and cause HO-1 induction (Meng et al., 2010). Arsenic has also been found to cause dysfunction in blood vessel relaxation and to cause vascular constriction (Lee et al., 2003).

Angiogenesis

Arsenic exposure has been linked with dysregulation of angiogenesis, the formation of new blood vessels from existing vessels in adult tissue (Liu et al., 2011). Dysregulation of angiogenesis has been observed in several cardiovascular diseases including atherosclerosis and ischemic heart disease (Loomans et al., 2004; Kao et al., 2003; Hayden and Tyagi, 2004; ATSDR, 1996).

Evidence in humans

In a cross-sectional study, (Osorio-Yáñez et al., 2013) investigated the association between iAs exposure, carotid intima thickness (cIMT), plasma asymmetric dimethylarginine (ADMA), and endothelial adhesion molecules in a pediatric population exposed to 3-135 ng/mL from Zimapan, Mexico. ADMA is a metabolic byproduct of protein modification processes and has been shown to inhibit nitric oxide (NO) synthesis resulting in decreases endothelial cell function. Increases in ADMA levels have been used to predict subsequent cardiovascular disease (Leong et al., 2008). The authors reported that increases in total arsenic (tAs) were associated with increased carotid intima thickness (cIMT) and increased ADMA. The authors also reported that plasma soluble vascular cell adhesion molecules (sVAM-1) along with cIMT, and percent tAs were significant predictors of ADMA levels (0.419 μmol/L increase in ADMA per 1 mm increase in cIMT). The reported increases in ADMA, sVAM-1, and cIMT were present in the absence of increases in serum lipids (Osorio-Yáñez et al., 2013), consistent with observations in other arsenic exposed human populations and in experimental animals (Simeonova et al., 2003; Hsueh et al., 1998).

Evidence in animals

Soucy et al. (2003) observed that C57BL/6 mice injected i.p. with 0.8, 8, or 80 µg/kg-day of sodium arsenite ($NaAsO_2$; equivalent to 0.8- 80 ppm) daily for three weeks had an increase in angiogenesis as measured by Matrigel mouse model. The authors found that FGF-2[16] (50 ng/mL) had a biphasic effect on blood vessel density when combined with low (0.8 µg/kg-day) and high (80 µg/kg-day) doses of iAs. Blood vessel density increased at these outermost iAs doses but remained unchanged at the intermediate dose. The authors only included luminal vessels containing fixed red blood cells in their quantification of vessels however, because not all capillaries contain red blood cells as some capillaries may be in a resting state or only partially perfused, meaning that they may not have had red blood cells at the time of observation. Also red blood cell distribution can be uneven (e.g., in areas with slower blood flow or in smaller vessels) and by including only luminal vessels containing red blood cells the authors could have missed capillaries and underestimated the total number of capillaries. By only considering vessels with fixed red blood cells, Soucy et al. (2003), may have missed a significant portion of the capillary network, resulting in a potential bias of the affect and interpretation of the study findings and conclusions. In a follow up study, Soucy et al. (2005) showed that C57BL/6NCr mice exposed to low-level arsenic exposure (0 to 50 ppb in drinking water) for five weeks formed enhanced neovascularization, the process of new blood vessels formation, in Matrigel at arsenic concentrations as low as 5 ppb (p <0.05). Enhanced neovascularization by arsenic could contribute to dysregulation of angiogenesis and contribute to the growth of atherosclerotic lesions and plaque formation (Khurana et al., 2005).

The study also showed that exposure of C57BL/6NCr mice to arsenic at higher doses for a greater duration (50-500 ppb iAs for five, ten, or twenty weeks) showed increased neovascularization. Significant dose dependent increases in neovascularization were observed at 5 weeks (50 ppb p <0.05; 250 ppb p <0.01; and 500 p <0.001). Significant increases in neovascularization were also observed at 10 weeks at all three exposure levels (50, 250, and 500 ppb iAs; p < 0.05). However, at 20 weeks, significant neovascularization was only observed in mice exposed to 50 and 250 ppb iAs in drinking water. No increased in neovascularization was observed at the 500 ppb iAs exposure level.

In damaged endothelium, VEGF, endothelin-1, and matrix metalloproteinases (MMPs) are induced in endothelial cells to facilitate angiogenesis. To probe the underlying mechanisms of the observed neovascularization, Soucy et al. (2005) showed that chronic arsenic exposure differentially affected angiogenic and remodeling gene expression. Early in the process (five weeks) arsenic increased the expression of VEGF, VEGF receptor 1 (VEGFR1), and PAI-1 in mice exposed to 250 and 500 ppb iAs. VEGF receptor 2 (VEGFR2) and MMP-9 expression increased at twenty weeks in the mice exposed to 50, 250, and 500 ppb iAs. Lastly, Endothelin-1 expression was

[16] Fibroblast growth factor 2 (FGF-2) can be used in Matrigel to model angiogenesis in mice (Claffey et al., 2001).

increased in mice exposed to 50 and 250 ppb iAs for twenty weeks. These results indicate that the underlying mechanism(s) involved in arsenic-stimulated angiogenesis may differ depending on iAs concentration and duration of exposure (Soucy et al., 2005).

Using liver as a model for studying the mechanisms by which inorganic arsenic affects vascularization and angiogenesis, Straub et al. (2008) showed that arsenic stimulated liver sinusoidal capillarization in mice was dependent on NAPDPH-oxidase generation of superoxide. Utilizing wildtype C57BL/6 mice, Straub et al. (2008) showed a significant dose-dependent decrease in porosity (described as percent open space in liver fenestrations relative to the area of vessel wall) and a dose-dependent increase in PECAM-1 expression in mice exposed to 0,10, 50, 100, or 250 ppb sodium arsenite in drinking water for two weeks ($p< 0.01$). Primary SECs exposed to 0, 1, 2.5, or 5 µM iAs for eight hours repeated the same pattern observed in vivo. Straub et al. (2008) also used $p47^{PHOX}$ knockout mice to study the effects of arsenic on vascularization and angiogenesis. p47 is a canonical essential cytosolic subunit of NOX-2-oxidase, $p47^{PHOX}$ knockout mice are unable to produce superoxide and have been used to study the role of p47phox in vascular dysfunction (Rezende et al., 2018; Chen and Stinnett, 2008). Straub et al. (2008) exposed $p47^{PHOX}$ knockout mice to 100 ppb in drinking water for two weeks did not have the decrease in porosity of the liver observed their wildtype counterparts. The attenuation of liver porosity in the $p47^{PHOX}$ knockout mice demonstrated that NADPH oxidase was required for arsenic- stimulated capillarization in vivo. These results were coherent or consistent in primary SECs derived from $p47^{PHOX}$ knockout animals exposed to 2.5 mM iAs (324.8 ppm) or 50 mM H_2O_2, for eight hours, where H_2O_2 but not iAs, decreased porosity in p47 null primary SECs. In addition, arsenic failed to increase nitrosylation in p47 null mice suggesting that superoxide (SO) generation and peroxynitrite formation are primary mechanisms involved in vasculature remodeling of the liver and impaired sinusoidal function observed in response to arsenic exposure (Straub et al., 2008).

Humanized rodent models such as apolipoprotein E knockout (ApoE-/-) mice have also been used to study the cardiometabolic effects of arsenic (Srivastava et al., 2009; Simeonova et al., 2003; Makhani et al., 2018; Lemaire et al., 2011). ApoE (-/-) mice are apolipoprotein E deficient and display poor lipoprotein clearance with subsequent accumulation of cholesterol ester-enriched particles in blood. The accumulation of these particles promotes the development of atherosclerotic plaques. The ApoE -/- mouse model has been well established for the study of human atherosclerosis as it emulates human lipid profiles and the anatomical localization and histopathological characteristics of the plaques that are produced in this mouse model more closely resemble human atherosclerosis as compared to other mouse models (eg., high-fat diet-induced mouse model (wild-type)). Simeonova et al. (2003) exposed female wild-type C57BL/6 and female ApoE -/- mice to 0, 20, or 100 ug/mL (0, 20 or 100 ppm) sodium arsenite in drinking water for 24 weeks. Transgenic animals exposed to sodium arsenite showed a dose dependent increase in atherosclerotic lesions covering the intimal area of the aorta versus nontreated transgenic mice (p <0.02) and Wildtype C57BL/6 animals exposed (treated and control). Further, the As-mediated

increases in atherosclerotic plaques were not accompanied with increased serum cholesterol, similar to observations of atherosclerosis in arsenic exposed, human populations (Hsueh et al., 1998). However, it was observed that atherosclerotic plaque progression was associated with the accumulation of arsenic in the cardiovascular tissue in the ApoE $^{-/-}$ mice (Simeonova et al., 2003), indicating a direct association with arsenic exposure. In a similar study, Lemaire et al. (2011) exposed male ApoE -/- mice to a much lower concentration of sodium arsenite (200 ppb for 13 weeks) and observed that the mice developed atherosclerotic lesions. The authors also reported that arsenic altered the plaque content; arsenic-induced plaques had decreased smooth muscle cells and collagen within the plaque making these plaques less stable, more susceptible to rupture and at increased risk of producing a myocardial infarct or stroke in humans. Additionally, the arsenic-induced plaques contained increased lipid content without increases in macrophages. In a follow up study, Makhani et al. (2018) exposed male ApoE -/- male mice to sodium arsenite in drinking water at doses ranging from 10 to 200 ppb (0, 10, 50, 100 or 200 ppb) for 13 weeks and observed a dose dependent increase in the size of the atherosclerotic plaques within the aortic sinus with significant differences from control mice starting at the lowest arsenic concentration tested ($p < 0.05$ at 10 ppb). The authors also analyzed the plaque content and observed that the components of the arsenic induced plaques had increased macrophage lipid accumulation, suggesting that macrophage-lipid homeostasis is sensitive to perturbation by arsenic (Makhani et al., 2018). In addition, the authors observed that arsenic-induced plaques had deceased smooth muscle cells and collagen content, making these plaques more susceptible to rupture and increasing risk for infarction and stroke, however these effects only reached statistical significance at the higher concentrations of arsenic exposure tested (100- 200 ppb).

Evidence from in vitro models

Straub et al. (2008) built on the work of Smith et al. (2001) and Lynn et al. (2000) showing that arsenic stimulates Nox-based oxidase activity through mobilization and activation of Rac-1-GTPase and increases Rac-1 association with sinusoidal endothelial cells (SEC) membranes during capillarization. In this study, Straub et al. (2008) showed that inhibition of Rac-1 GTPase provided protection from arsenic stimulated defenestration in SECs.

Hays et al. (2008) investigated early events in arsenic-induced vascular pathology. C57BL/6 male mice were exposed to 0 or 50 ppb sodium arsenic in drinking water for four, five, or eight weeks. The lungs from the experimental animals were excised and gene expression changes were measured using Affymetrix mouse array. The authors did not report any statistical significance in gene expression in any of the animals exposed to arsenic compared to control (Hays et al., 2008).

Risk Modifiers

A review of the epidemiological studies discussed in this section, along with studies identified from a targeted literature search on modifying factors (see Section 3.10 of iAs Protocol)

identified in Table 3-2, suggest that the following factors increase the risk of arsenic-associated cardiovascular effects:

- **Methylation capacity:** Individuals who metabolize iAs to MMA and DMA less efficiently have an increased risk of arsenic-induced cardiovascular disease. This is based on findings—from multiple studies across a wide range of populations—that derive indicators of methylation capacity from the concentrations of arsenic metabolites found in urine. These studies indicate that lower methylation capacity increases the risk of arsenic-associated cardiovascular effects including IHD and hypertension. Supporting evidence is provided by studies reporting that the risk of arsenic-associated cardiovascular outcomes is modified by polymorphisms linked to methylation capacity. A case-cohort analysis of a large Bangladesh population studied by Chen et al. (2011b) reported increased risk of IHD-related mortality among those with lower methylation capacity, suggesting that low methylation capacity may increase the risk of arsenic-associated mortality (Chen et al., 2013c)

- **Smoking:** Smoking increases the risk of arsenic-associated cardiovascular effects and smokers are a susceptible population. Two prospective cohort studies of iAs and CHD-related mortality reported effect modification by smoking status. An interaction was detected between iAs concentration in drinking water and current smoking in the HEALS cohort of Bangladesh (Chen et al., 2011b). In this study, the relative excess risk for interaction comparing ever to never smokers were 1.56 (95% CI: 0.05–3.14). In a longitudinal analysis of data from the New Hampshire Skin Cancer Study, a population-based cohort study, Farzan et al. (2015a) reported an association of CVD with toenail arsenic in current smokers (HR = 1.69, 95% CI: 1.04–2.75) but not in never smokers (HR = 0.84, 95% CI: 0.58–1.21). Similar results were obtained when smoking status was defined as years of smoking or pack-years. In addition, the association observed between arsenic exposure and cIMT thickness was greater among smokers (Chen et al., 2013b).

- **Genetic variation:** Although the evidence is limited, several studies suggest that genes related to the regulation of atherosclerosis might increase the risk of arsenic-associated cardiovascular effects. Several epidemiological studies (see Table 3-2) examined the interaction between arsenic exposure and various polymorphisms that increased the risk of cardiovascular endpoints, including electrocardiogram abnormality, carotid atherosclerosis, coronary heart disease, cIMT, and hypertension. Genetic variants may also alter the metabolism of inorganic arsenic independently of excretion or absorption (e.g., glutathione *S*-transferase (GST), arsenic 3+ methyl transferase (AS3MT)) leading to increased susceptibility.

- **Life stages:** Although the evidence is limited, several studies suggest that early life represents a susceptible lifestage for arsenic exposure and subsequent myocardial infarction. Studies (see Table 3-2) have also reported increased blood pressure and cIMT among children exposed to arsenic during early life (in utero and during early childhood).

- **Nutrition:** Although the evidence is limited, several studies suggest that those with nutrient deficiencies are a susceptible population with respect to arsenic exposure and subsequent hypertension. One study indicates that hypertension is associated with iAs only among those deficient in vitamin B and folate.

- **Sex:** Overall, neither males nor females clearly represent a susceptible population. Several studies have evaluated sex as a modifier of the association between arsenic exposure and various cardiovascular outcomes. Although risk estimates sometimes differed in males compared with females in some studies, no overall pattern emerges suggesting that either sex is more susceptible to the effects of arsenic exposure on CVD and related outcomes.

Table 3-2. Risk modifiers for cardiovascular disease from targeted search

Modifying factor	Key reference	Effect	Population, exposure level
Methylation capacity	Wu et al. (2006)	Increased risk of carotid atherosclerosis (OR = 2.7, 95% CI: 1.0–7.8) in residents with arsenic exposure >100 µg/L with plasma homocysteine levels ≥12.7 µmol/L and monomethylarsonic acid (MMA) ≥16.5% compared with those with plasma homocysteine levels <12.7 µmol/L and MMA <16.5% (OR = 1.7, 95% CI: 0.6–5.2)	Taiwan, <50–>100 µg/L (water)
	Tseng et al. (2005)	Increased risk of peripheral vascular disease in residents with cumulative arsenic exposure >100 µg/L-yr and for PMI >1.77 and SMI >6.93 (OR = 2.93 95% CI: 0.90–9.52), PMI >1.77 and SMI ≤6.93 (OR = 2.85, 95% CI: 1.05–7.73), PMI ≤0.77 and SMI ≤6.93 (OR = 3.60, 95% CI: 1.12–11.56)	Taiwan, 700–930 µg/L (median water)
	Wang et al. (2011)	Significant association reported between lower methylation capacity (indicated by higher urinary concentrations of arsenate) and increased risk of hypertension; potential synergistic effect also observed between lower methylation capacity and higher BMI, and increased odds of hypertension	Taiwan, 700–930 µg/L (median water)
	Chen et al. (2013b)	Positive association between arsenic exposure and increase in carotid intima-media thickness and for every 10% increase in urinary MMA, 12.1-µm increase (95% CI: 0.4–23.8) in carotid intima-media thickness	Bangladesh, 81.1 µg/L (mean water)
	Li et al. (2013a)	Significant negative relationship between hypertension and % DMA (adjusted OR = 0.036, 95% CI: 0.002–0.822) for arsenic exposure >50 µg/L	China, <10–>50 µg/L (water)
	Li et al. (2013b)	Residents with higher MMA levels had significantly increased risk for hypertension (OR = 1.693, 95% CI: 1.028–2.787) compared with those with lower MMA levels, and those with higher DMA levels had decreased risk of hypertension (OR = 1.549, 95% CI: 0.938–2.559) compared with those with lower levels of DMA	China, 0–650 µg/L

Modifying factor	Key reference	Effect	Population, exposure level
	Li et al. (2015)	Significantly higher odds of hypertension among individuals with low methylation capacity (indicated by lower DMA% and SMI) compared with subjects with indicators of higher methylation capacity; potential synergistic effects also observed between lower methylation capacity and older age, higher BMI, and smoking, and increased odds of hypertension	China, <0–760 µg/L range (water)
	Farzan et al. (2015b)	Associations were reported between urinary arsenic and blood pressure among both those with higher PMI or higher SMI	United States, 0.35 to 288.5 µg/L range (water)
Smoking	Chen et al. (2011b)	Significant synergistic effect between arsenic exposure and smoking and increased mortality from ischemic heart disease and other heart disease	Bangladesh, <12–>148 µg/L (water)
	Tseng et al. (2005)	No increased risk from smoking for peripheral vascular disease associated with arsenic exposure	Taiwan, 700–930 µg/L (median water)
	Farzan et al. (2015a)	Significantly increased risk of mortality due to ischemic disease among current smokers compared with never smokers, and those reporting ≥31 yr or ≥30 pack-yr of smoking, respectively, compared with 0 pack-yr of smoking	United States, 0–158.1 µg/L range (water)
Genetic Variation	Liao et al. (2009)	Polymorphisms in two paraoxonase genes (PON1 and PON2) and cumulative arsenic exposure >14,700 µg/L-yr associated with increased risk of electrocardiogram abnormality	Taiwan, 350–1,140 µg/L (water, 1960s)
	Li et al. (2009)	No significant association between atherosclerosis and cumulative arsenic exposure >15,000 µg/L-yr with four polymorphisms of the PON genes (PON1-108C/T, PON1 Q192R, PON2 A148G, PON2 C311S)	Taiwan, <100–>15,000 µg/L (water)
	Hsieh et al. (2008b)	Increased risk of carotid atherosclerosis with arsenic exposure >10 µg/L and polymorphisms in apolipoprotein E (APOE) (epsilon 4 allele) and monocyte chemoattractant protein-1 (MCP-1) (A/G or G/G)	Taiwan, <10–>50 µg/L (water)
	Chiou et al. (2001b)	Increased risk of carotid atherosclerosis with arsenic exposure >50 µg/L and polymorphisms of glutathione S-transferase (GSTM1, GSTT1, and GSTP1)	Taiwan, <0.15–3,590 µg/L (water)
	Wang et al. (2007)	Increased risk of carotid atherosclerosis with arsenic exposure >50 µg/L and GSTP variant (Ile/Val and Val/Val) and p53 variant (Arg Pro and Pro/Pro) genotypes	Taiwan, <10–>50 µg/L (water)

Modifying factor	Key reference	Effect	Population, exposure level
	Wu et al. (2010b)	Absence of class S allele of heme oxygenase-1 (HO1) gene with arsenic exposure >750 µg/L associated with increased risk of carotid atherosclerosis	Taiwan, <10–>750 µg/L (water)
	Wu et al. (2010a)	Significantly reduced risk of coronary heart disease, cerebrovascular disease, and peripheral arterial disease with arsenic exposure <150 µg/L for carriers of the L/S or S/S genotypes of the HO-1 gene compared with noncarriers	Taiwan, <50–>300 µg/L (water)
	Wu et al. (2011)	Reduced risk of cardiovascular-related mortality in hypertensive subjects with median arsenic exposure of 221–326 µg/L with the S allele genotype of the HO-1 gene compared with those without the S allele	Taiwan, <50–>750 µg/L (water)
	Hsieh et al. (2011)	Increased risk of carotid atherosclerosis with arsenic exposure >50 µg/L and PNP A-T haplotype and either the AS3MT genotype TC or glutathione S-transferase omega 1 (GSTO) haplotypes CAA/ht3 (CAG) or AGG	Taiwan, <10–>50 µg/L (water)
	Wu et al. (2014)	Increased risk of cIMT with arsenic exposure ≥40.4 µg/L and polymorphisms in APOE, arsenic 3-methyltransferase (AS3MT), purine nucleoside phosphorylase (PNP), and tumor necrosis factor (TNF) genes	Bangladesh, 76.4 µg/L (mean water)
	Farzan et al. (2015c)	Higher annual pulse pressure associated with arsenic exposure and CYBA rs3794624 variant genotype after adjustment for multiple testing	Bangladesh, 102.0 µg/L normal SBP; 91.9 µg/L pre-hypertensive to hypertensive (mean water)
	Hsueh et al. (2005)	Increased risk of hypertension with cumulative arsenic exposure ≥10,500 µg/L-yr and polymorphisms of manganese superoxide dismutase (MnSOD) (T-to-C substitution in mitochondria targeting sequence), NADPH oxidase (C-to-T substitution of the C242T site), and endothelial nitric oxide synthase (eNOS) (G-to-T substitution of G894T site)	Taiwan, 700–930 µg/L (median water)
Life stages	Yuan et al. (2007)	Higher risks for mortality from acute myocardial infarction (mortality rate ratio = 3.23, 95% CI: 2.79–3.75) for men 30 to 49 yr of age exposed in utero or in childhood to approximately 580 µg/L arsenic compared with those not exposed in utero or in childhood	Chile, 580 µg/L (mean water 1958–1970)

Modifying factor	Key reference	Effect	Population, exposure level
	Tseng et al. (2005)	Significantly increased risk of peripheral vascular disease in older compared with younger residents, likely due to older resident's decreased capacity to methylate arsenic to DMA	Taiwan, 700–930 µg/L (median water)
	Smith et al. (2012)	Significantly higher risk for mortality from acute myocardial infarction (standardized mortality ratio = 2.1, 95% CI: 1.8, 2.5) for residents 30 to 49 yr of age exposed in utero or in childhood during the high-exposure period (1958–1970) compared with the general population	Chile, mean drinking water: before 1958: 90 µg/L; 1958–1970: 870 µg/L; 1970–1980: 110 µg/L; 1980–2012: <10 µg/L
Nutrition	Chen et al. (2007)	Subjects with below average dietary intake of vitamin B and folate had an increased risk of hypertension with increasing arsenic levels	Bangladesh, 0.1–684 µg/L (water)
Sex	Lewis et al. (1999)	No difference in hypertensive heart disease between men (SMR = 2.20, 95% CI: 1.36–3.36) and women (SMR = 1.73, 95% CI: 1.11–2.58), but association for all other heart disease increased in women only (SMR 1.43 compared with 0.94 in men)	United States, 14–166 µg/L (median water)
	Tollestrup et al. (2003)	Significantly elevated hazard ratio (HR = 1.77, 95% CI: 1.21–2.58) for ischemic heart disease for boys living more than 10 yr <1.6 km from copper smelter and arsenic refinery site, but not elevated (HR = 1.69, 95% CI: 0.81–3.51) in girls	United States, <1.0–>10 yr (# yr spent at residence)
	Tseng et al. (2005)	Significantly increased risk for peripheral artery disease in men compared with women, reportedly due to women's increased capacity to methylate arsenic to dimethylarsenic acid (DMA)	Taiwan, 700–930 µg/L (median, water)
	Rahman et al. (2014)	Significantly increased risk of stroke with arsenic exposure >50 µg/L for the whole population (HR = 1.35, 95% CI: 1.04–1.75) and women alone (HR = 1.72, 95% CI: 1.15–2.57) but not for men alone (HR = 1.07, 95% CI: 0.75–1.51)	Bangladesh, <10–>50 µg/L (water)
	D'Ippoliti et al. (2015)	Significantly increased risk of mortality due to myocardial infarction and peripheral arterial disease, respectively, with cumulative arsenic exposure in males but not in women; a higher risk of mortality due to stroke in women compared with men	Italy, 0.5–80.4 µg/L (water)

Evidence Judgment

A large robust body of epidemiological studies supports the conclusion that the currently available **evidence demonstrates** that iAs causes DCS in humans (see Table 3-3) given sufficient exposure conditions.[17] This is consistent with the conclusion of the NASEM, which rated IHD as Tier 1 based on the strength of the evidence (NRC, 2013). The evidence from the large *high* and *medium* confidence longitudinal studies consistently reported associations with IHD incidence and mortality, while the results for hypertension were also largely consistent. These large studies were conducted in different countries and studied populations with high and low (<100 μg/L) arsenic concentrations in drinking water. (Supplemental figures of results from studies documenting adverse effects from exposure to inorganic arsenic in drinking water at concentrations less than or equal to 100 μg/L, as described in 1.6.3, are available in Appendix B.5.). The studies adjusted for key confounders including BMI, smoking status, and education level, potential risk factors for ischemic heart and cardiovascular disease that may be related to the distribution of arsenic or influence health effects of arsenic exposure.

Consistent exposure-dependent associations of iAs concentration in drinking water with IHD-related morbidity and mortality were observed (Figure 3-5). There is evidence of a *dose-response gradient* across studies, including IHD incidence and mortality, CVD, hypertension, atherosclerosis, and electrocardiogram abnormalities. The evidence is from several studies with longitudinal designs that establish the temporality between exposure and effect, and in which important confounding factors were controlled in the analyses (Farzan et al., 2015a; James et al., 2015; Moon et al., 2013; Chen et al., 2011b; Sohel et al., 2009). Consistent evidence from epidemiological studies of associations between iAs and increases in cIMT, an indicator of preclinical atherosclerosis, provides coherence and biological plausibility for associations with cardiovascular-related morbidity and mortality (Chen et al., 2013b; Osorio-Yáñez et al., 2013; Chiou et al., 2001b; Chen et al., 2013b; Chiou et al., 2001b; Osorio-Yáñez et al., 2013). Larger effect estimates among those with genotypes linked to regulation of atherosclerosis also support the biological plausibility for observed associations (Chen et al., 2012b; Huang et al., 2009; Li et al., 2009).

As shown in Figure 3-10 and Figure 3-11, associations between iAs exposure and hypertension, which is a risk factor for IHD, were fairly consistent. Although no association of time-weighted average iAs exposure with hypertension was observed in the HEALS cohort of Bangladesh, associations with increased SBP and DBP (Jiang et al., 2015; Jiang et al., 2015) and PP in subgroups with low nutrient intake (Chen et al., 2007; Chen et al., 2007) were observed. In addition, exposure to arsenic was associated with increased blood pressure in a prospective cohort of pregnant women in the New Hampshire Birth Cohort (Farzan et al., 2015b) (well water concentration mean(SD): 4.3(11.0) μg/L), and cross-sectionally in children in Mexico (drinking

[17]The term, "sufficient exposure conditions," is discussed and defined for the identified health effects in the dose-response analysis in Section 4.

water-arsenic concentrations ranging from 3 to 135 μg/L) (Osorio-Yáñez et al., 2015). Other lines of evidence are limited but provide some support for coherence and biological plausibility for an effect of iAs exposure on blood pressure. Associations with endpoints indicating sympathetic hyperreactivity, which are considered early risk factors for hypertension, are reported in an arsenic-exposed population of normotensive men in Romania (Kunrath et al., 2013). Associations between iAs and QT prolongation in humans, which co-occurs with LVH and hypertension, also lend additional support to the overall evidence of an iAs effect on hypertension (Chen et al., 2013d; Mordukhovich et al., 2009; Wang et al., 2009).

Some evidence from epidemiological studies indicates iAs exposure could be associated with cerebrovascular disease and stroke, although findings across the available studies on this outcome are largely inconsistent. An association of stroke-related mortality was observed in a prospective study in Bangladesh where concentrations of iAs in drinking water ranged from 0.5 to 644 μg/L (median 86.8) (Rahman et al., 2014); and in Italy where arsenic concentrations were lower (mean 19.3 μg/L) (D'Ippoliti et al., 2015). Positive, imprecise, or null associations were observed across other studies of varying design, however.

Overall, there is *robust* evidence from a large set of *high* and *medium* confidence epidemiological studies of varied design showing that the currently available **evidence demonstrates** that iAs exposure causes DCS in humans given sufficient exposure conditions. This conclusion is based on studies of humans that assessed a variety of exposure levels (e.g., including < 20 μg/L). The strongest evidence derives from studies of IHD incidence and mortality and, to a lesser extent, hypertension. Coherent evidence is provided by studies linking arsenic exposure to related conditions such as atherosclerosis and repolarization abnormalities. The epidemiological evidence base includes multiple, large, high-quality longitudinal studies that control for important confounders and adequately consider other forms of bias. Diseases of the circulatory system are therefore considered for dose-response analysis as discussed in Section 3.3 (Hazard Considerations for Dose-Response Analysis) and Section 4 (Dose-Response Analysis).

Table 3-3. Evidence profile table for epidemiological evidence on iAs and diseases of the circulatory system

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
Studies	**Summary of key findings**	**Factors that increase certainty**	**Factors that decrease certainty**	**Evidence synthesis judgment(s)**
Cardiovascular disease; Ischemic heart disease 25 *medium* or *high* confidence studies	Large, prospective cohort studies support exposure-dependent associations of relatively low exposures to iAs in drinking water (<100 µg/L) with incidence and mortality; associations observed in other study design including cross-sectional, and ecological "natural experiments" across populations including U.S., Bangladesh, China, Taiwan, and Mexico.	• Studies are *medium* or *high* confidence. • Consistency – within and across study types, including meta-analyses. • Dose-response gradient – observed in most studies. • Large or concerning magnitude of effect – large odds ratios (e.g., >4–6) in some studies. • Coherence with findings for related endpoints/IHD risk factors such as hypertension, atherosclerosis	• No factors noted.	⊕⊕⊕ *Robust*
Hypertension 31 *medium* or *high* confidence studies	Cohort studies across geographically diverse populations report positive associations, which might be more pronounced with higher exposure (>50 µg/L).	• Studies are *medium* or *high* confidence. • Consistency – generally reported with metrics indicating recent exposure to iAs (or cumulative exposure in currently exposed populations) across different	• No factors noted.	⊕⊕⊕ *Robust*

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
		life stages, including adults, pregnant women, and children. • Dose-response gradient observed in most studies. • Large or concerning magnitude of effect – large odds ratios (e.g., >2–4) in some studies. • Coherence across related endpoints such as QT prolongation		
Cerebrovascular disease and stroke 11 *medium* or *high* confidence studies	Some well-conducted studies report positive associations. However, inverse or null associations were also observed across other studies of varying design.	• Studies are *medium* or *high* confidence. • Dose-response gradient observed in many studies, though more consistently observed in populations with higher (>100 µg/L) concentrations of iAs in drinking water	• Unexplained inconsistency across studies	⊕⊕⊙ *Moderate*

3.2.2. Diabetes

Database Overview

In 2013, the NRC concluded that low-to-moderate levels of inorganic arsenic are associated with diabetes based on evidence from human studies (NRC, 2013). As a result, evaluation of diabetes was categorized as a priority outcome and recommended for consideration for dose-response analysis in the IRIS Toxicological Review. On the basis of on the analysis of epidemiological evidence, the strength of evidence judgment for a causal association was considered "robust." *Robust* evidence from humans leads to the strongest evidence integration conclusion of **evidence demonstrates** (U.S. EPA, 2022). This section summarizes the review of the currently available evidence demonstrating that iAs causes type 2 diabetes in humans.

There are 112 epidemiologic publications that report on the relationship between arsenic exposure and diabetes (see Figure 3-22). Fifty-seven of the 112 studies were considered medium or high confidence, 13 were considered low confidence due to limitations noted in HAWC, and 41 studies identified in the 2022 search update were considered further for dose-response but were not factored into the qualitative considerations and synthesis (see Section 1.6.1). Because of the abundance of the evidence base, the subsequent synthesis is focused on the medium and high confidence studies (see Figure 3-23 and Figure 3-24). Citations of studies broken down by confidence level and studies identified in the 2022 update can be accessed via the interactive HAWC literature tag-tree visual presented in Figure 3-22. While the majority of these epidemiologic studies examined drinking water exposure to arsenic; others reported arsenic levels in biomarkers of exposure such as urine and blood. Further, epidemiologic data related to risk modifiers (e.g., genetic variation, cigarette smoking) are also presented. The information below is organized by study design.

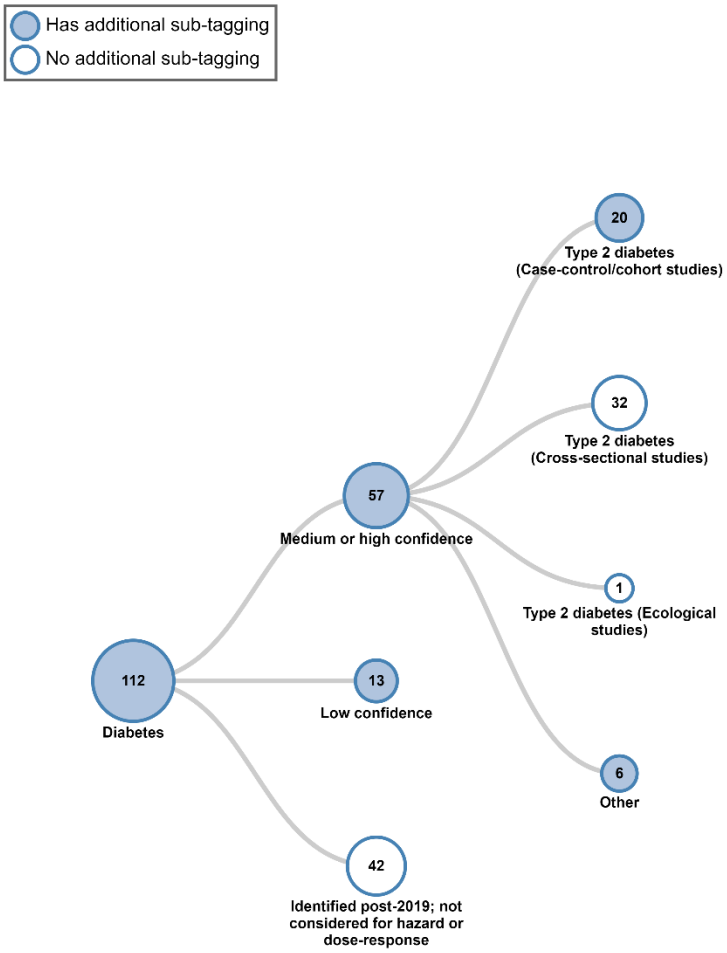


Figure 3-22. Literature tree of epidemiological studies that assessed diabetes (see interactive version in HAWC).

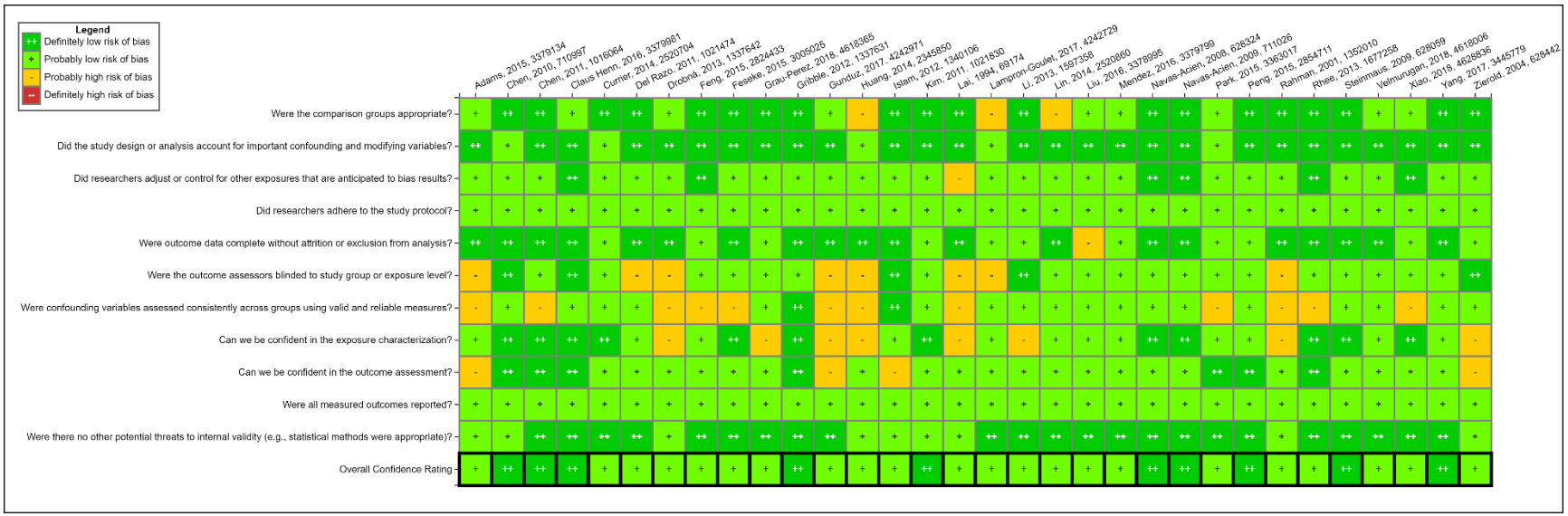


Figure 3-23. Study evaluation ratings for cross-sectional studies evaluating diabetes (see interactive version in HAWC).

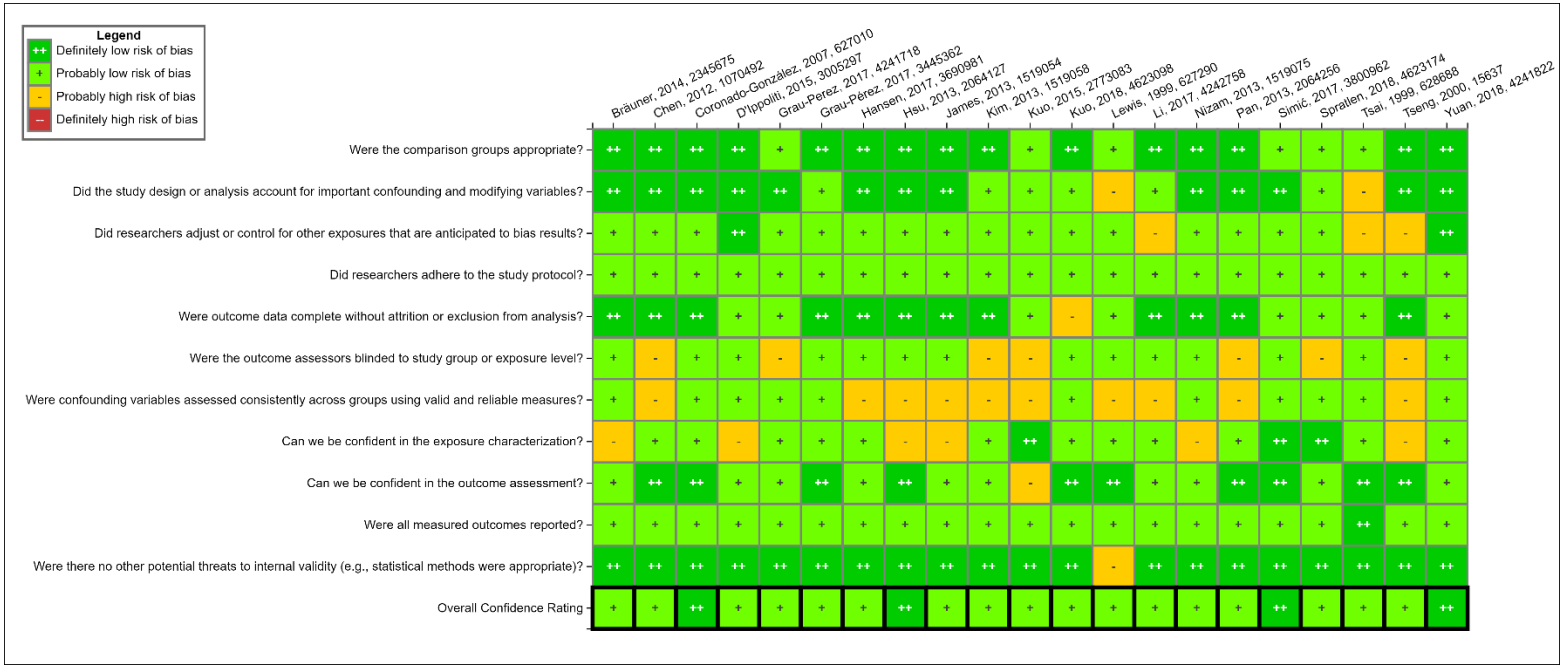


Figure 3-24. Study evaluation ratings for case-control, cohort, and ecological studies evaluating diabetes (see [interactive version in HAWC]).

Evidence from Epidemiological Studies

Studies used a variety of methods to determine diabetes status; diabetes was defined based on several diagnostic measurements or conditions, including level of fasting glucose or 2-hour glucose measurements, HbA1c values, glucosuria, metabolic syndrome, insulin levels, impaired glucose tolerance, self-reported physician diagnosis, current use of diabetes medication, and insulin resistance. Almost all studies required participants to have one validated clinical indicator of a diabetes diagnosis based on WHO or American Diabetic Association criteria. For this evaluation, glucosuria, defined as excretion of glucose in the urine, was not considered an adequate diagnostic indicator of diabetes status. Studies that used this diagnostic indicator as the sole criterion for diabetes diagnosis were considered *critically deficient,* rated as low and not considered further (Guo et al., 2007). Results, discussion, and evidence judgment focus on type 2 diabetes, as the evidence base is primarily for this outcome. Type 1 diabetes and gestational diabetes studies are included in study evaluation but are discussed in the 'Other' category.

Overall, the association between arsenic exposure and diabetes was mostly positive and consistent across studies (see Figure 3-25 and Figure 3-26). The strongest evidence comes from cohort and case-control studies, which generally demonstrated a positive association between arsenic exposure and incidence of diabetes mellitus or diabetes-related mortality (D'Ippoliti et al., 2015; Shapiro et al., 2015; Farzan et al., 2016). Most studies adjusted for relevant confounders (e.g., age, sex, BMI, smoking) and still observed an independent association with arsenic. The included studies were conducted in the general population of the United States as well as in both the general population and in occupational settings in various regions of the world including Bangladesh, Taiwan, China, Canada, Denmark, Italy, and Mexico.

Case-control and cohort studies

The literature review identified 20 case-control and cohort *medium* or *high* confidence studies (Yuan et al., 2018; Tseng et al., 2000; Spratlen et al., 2018; Simić et al., 2017; Pan et al., 2013b; Nizam et al., 2013; Li et al., 2017; Lewis et al., 1999; Kuo et al., 2015; Kuo et al., 2018; Kim et al., 2013; James et al., 2013; Hsu et al., 2013; Grau-Pérez et al., 2017; Grau-Perez et al., 2017; D'Ippoliti et al., 2015; Coronado-González et al., 2007; Chen et al., 2012a; Bräuner et al., 2014) that evaluated the association between iAs exposure and type 2 diabetes. The findings generally demonstrated a positive association between arsenic exposure and incidence of diabetes; the hazard ratios were usually around 2 when compared with those in lowest exposure category, often ≤10 µg/L (see Figure 3-25). A dose-response gradient was observed within some [e.g., (Pan et al., 2013b; James et al., 2013; Grau-Perez et al., 2017; Ettinger et al., 2009; D'Ippoliti et al., 2015; Coronado-González et al., 2007; Chen et al., 2012a; Bräuner et al., 2014)] but not all studies, with stronger effects observed in higher exposure regions. While many of these studies examined drinking water exposure to arsenic as a function of consumption duration and well arsenic concentrations, Tseng et al. (2000) conducted a prospective cohort study in an arseniasis-endemic

village of Taiwan and identified a positive dose-response relationship between arsenic ingestion and diabetes incidence with a relative risk (RR) of 2.1 (95% CI: 1.1, 4.2) for cumulative drinking water exposures ≥17,000 μg/L*year. In Denmark, Bräuner et al. (2014) conducted a prospective cohort study that identified an incidence rate ratio (IRR) of 1.03 (95% CI: 1.01, 1.06) per 1-μg/L increase in average arsenic drinking water levels when diabetes diagnoses were defined by blood glucose levels, use of diabetes medication, and other inclusion criteria of the Danish National Diabetes Register. However, when a stricter definition of diabetes was used (i.e., when cases were excluded if diabetes was defined only by blood glucose levels), the RRs were somewhat attenuated (IRR = 1.02; 95% CI: 0.99, 1.05). When the study population was evaluated by quartiles, the IRR was 1.19 (95% CI: 1.09, 1.31) in the highest quartile of exposure (>1.82 μg/L) compared with the lowest exposure group (<0.57 μg/L). In a Chinese population, a case-control study (Li et al., 2017) found plasma arsenic (median: 0.615 μg/L) to be associated with diabetes mortality, while another case-control study (Yuan et al., 2018) observed a null association between plasma arsenic concentrations (median (IQR): 2.04 (1.25, 3.63) μg/L) and type 2 diabetes among Chinese senior adults.

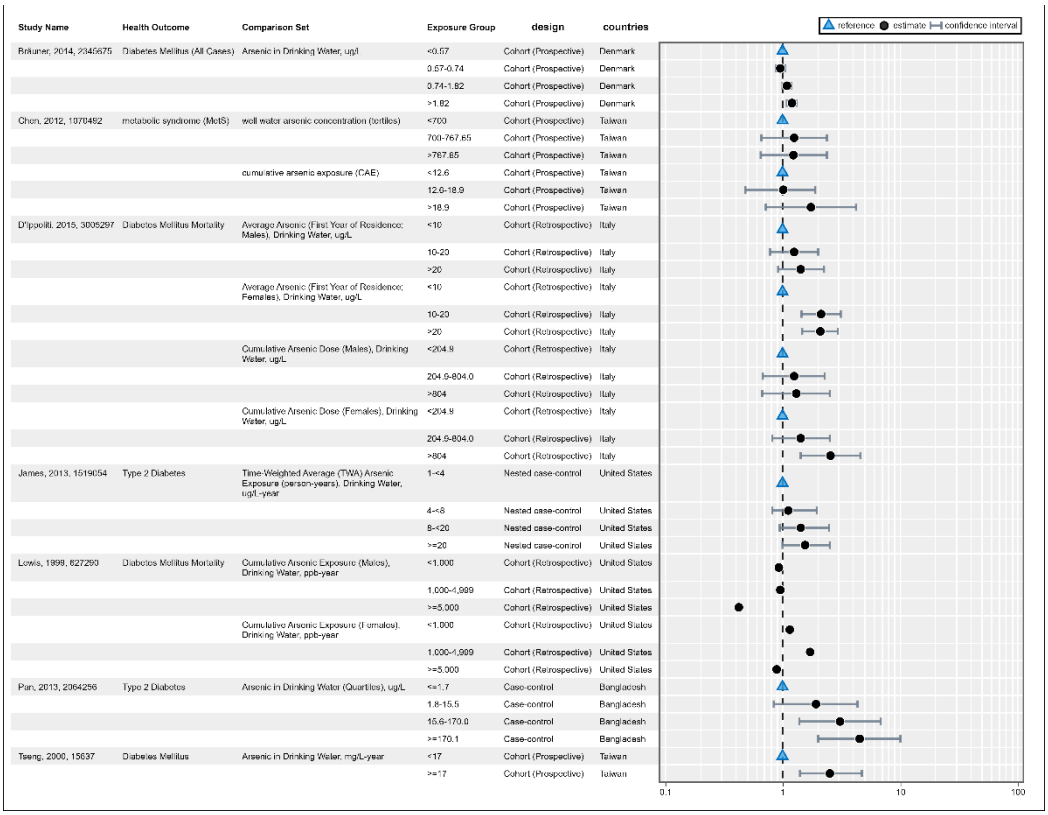
Grau-Perez et al. (2017) also evaluated the prospective association of arsenic exposure and metabolism with type 2 diabetes and insulin resistance (IR) in the SHFS. Incident diabetes status was determined by HOMA2-IR (fasting glucose ≥126 mg/dL), self-reported physician diagnosis or self-reported use of insulin or oral diabetes treatment. Median urine ∑As a baseline was 5.9 μg/L. The authors reported that over 10,327 person-years of follow-up, 252 participants developed diabetes (N = 1,838). Median HOMA2-IR at baseline was 1.5. The hazard ratio [95% (CI)] for incident diabetes per an interquartile range increase in ∑As was 1.57 (95% CI: 1.18, 2.08) in participants without prediabetes at baseline. The authors found that while iAs metabolism was not associated with incident diabetes, arsenic metabolism with HOMA2-IR results differed among study participants according to vitamin B intake and AS3MT genetic variant, indicating a role for nutrition as a risk modifier. Finally, ∑As was positively associated with HOMA2-IR at baseline but negatively with HOMA2-IR at follow-up (initial 2–3 years and 7–10 years). Increased MMA% was associated with lower HOMA2-IR when either iAs% or DMA% decreased. Further, a positive association was observed between arsenic exposure and incident diabetes among participants without baseline prediabetes and a cross-sectional and prospective association was observed between low MMA% and higher HOMA-IR measures, but not with incident diabetes. Kuo et al. (2018), a 15-year birth cohort follow-up study in Taiwan, did not find significant associations between postnatal iAs exposure (median urinary arsenic at age 2: boys: 22.3 μg/L; girls: 17.7 μg/L) and adolescent HOMA-IR.

One study of metabolic syndrome, a related outcome defined as having at least three of five risk factors: large waistline, high triglycerides, low HDL, high blood pressure, and high fasting blood sugar, reported no association (Chen et al., 2012a). The authors also measured insulin sensitivity (Chen et al., 2012a). While an increase was observed in the OR for metabolic syndrome (1.73 for

cumulative arsenic >18,900 µg/L*yr [versus <12,600 µg/L*yr] and 1.24 for well water arsenic concentration >767.65 µg/L [versus <700 µg/L]), the results were not statistically significant and may be due to a smaller sample size relative to other studies (N = 287). There also was not a correlation between cumulative arsenic exposure and insulin sensitivity. A more recent prospective cohort study by Spratlen et al. (2018) evaluated the associations of baseline arsenic exposure (i.e., urinary arsenic levels, median(IQR): 6.5 (4.2–10.8) µg/L) and metabolism (relative percentage of arsenic species over their sum, (∑As)) with incident metabolic syndrome (MetS) and its individual components (i.e., elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, and elevated fasting plasma glucose) in the Strong Heart Family Study (SHFS).[18] The authors found that an interquartile range increase in ∑As arsenic exposure was associated with a 1.19-fold (95% Cl: 1.01, 1.41) greater risk of elevated fasting plasma glucose concentration but not with other individual components of the MetS or MetS overall.

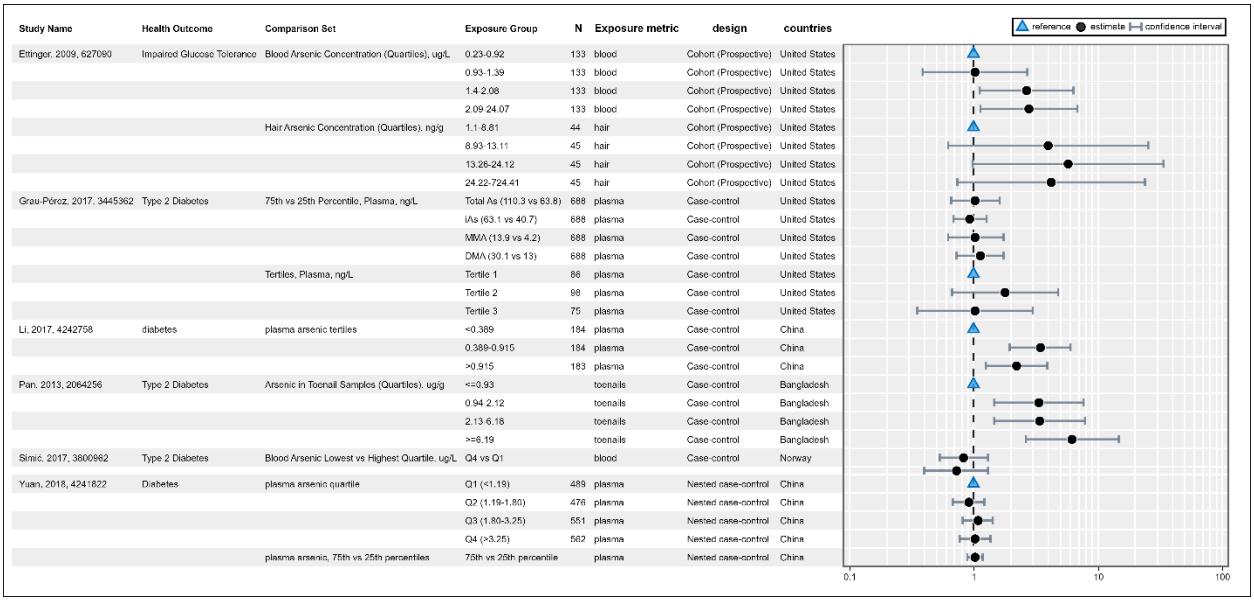
Evidence from retrospective cohort studies also largely reported a positive association between arsenic exposure and diabetes. D'Ippoliti et al. (2015) reported an association between cumulative arsenic (CAI) exposure levels >804.0 µg with diabetes mortality in females (hazard ratio (HR) of 2.56 CI: 95% 1.43, 4.57 $p < 0.001$).[19]

[18]The SHFS is an extension of the Strong Heart Study (SHS), a population-based study of American Indian adults in which relatives of the SHS participants were recruited.
[19]A statistically significant association between iAs exposure and diabetes mortality was only observed in female but not in male individuals in this study.



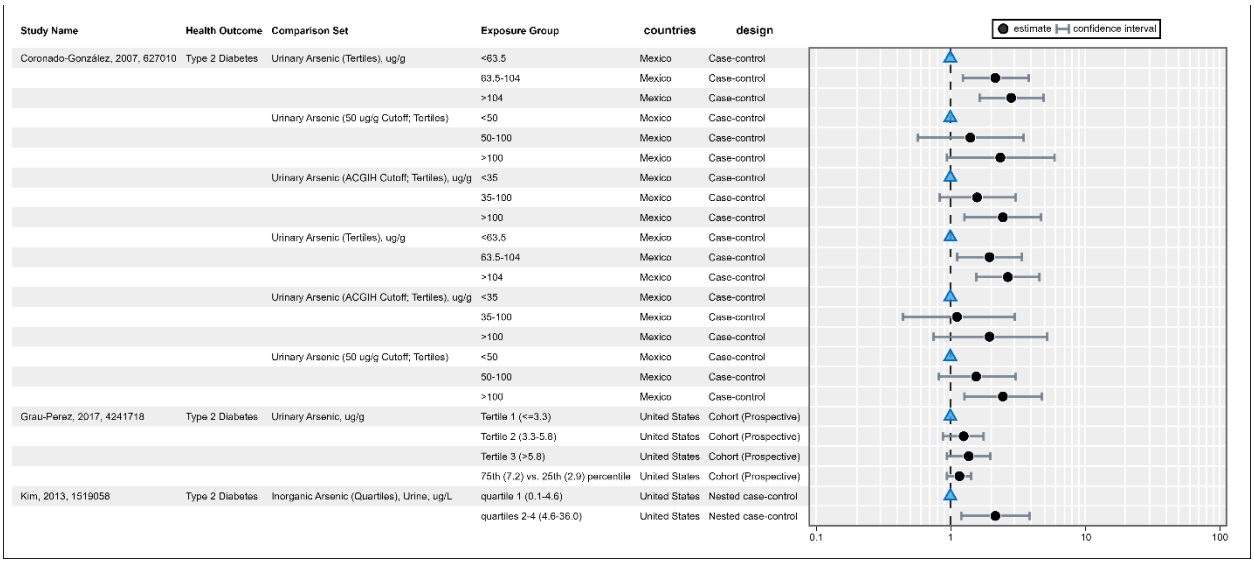
Study Name	Health Outcome	Comparison Set	Exposure Group	design	countries
Brüner, 2014, 2345675	Diabetes Mellitus (All Cases)	Arsenic in Drinking Water, ug/l	<0.57	Cohort (Prospective)	Denmark
			0.57-0.74	Cohort (Prospective)	Denmark
			0.74-1.82	Cohort (Prospective)	Denmark
			>1.82	Cohort (Prospective)	Denmark
Chen, 2012, 1070482	metabolic syndrome (MetS)	well water arsenic concentration (tertiles)	<700	Cohort (Prospective)	Taiwan
			700-767.65	Cohort (Prospective)	Taiwan
			>767.65	Cohort (Prospective)	Taiwan
		cumulative arsenic exposure (CAE)	<12.6	Cohort (Prospective)	Taiwan
			12.6-18.9	Cohort (Prospective)	Taiwan
			>18.9	Cohort (Prospective)	Taiwan
D'Ippoliti, 2015, 3005297	Diabetes Mellitus Mortality	Average Arsenic (First Year of Residence; Males), Drinking Water, ug/L	<10	Cohort (Retrospective)	Italy
			10-20	Cohort (Retrospective)	Italy
			>20	Cohort (Retrospective)	Italy
		Average Arsenic (First Year of Residence; Females), Drinking Water, ug/L	<10	Cohort (Retrospective)	Italy
			10-20	Cohort (Retrospective)	Italy
			>20	Cohort (Retrospective)	Italy
		Cumulative Arsenic Dose (Males), Drinking Water, ug/L	<204.9	Cohort (Retrospective)	Italy
			204.9-804.0	Cohort (Retrospective)	Italy
			>804	Cohort (Retrospective)	Italy
		Cumulative Arsenic Dose (Females), Drinking Water, ug/L	<204.9	Cohort (Retrospective)	Italy
			204.9-804.0	Cohort (Retrospective)	Italy
			>804	Cohort (Retrospective)	Italy
James, 2013, 1519054	Type 2 Diabetes	Time-Weighted Average (TWA) Arsenic Exposure (person-years), Drinking Water, ug/L-year	1-<4	Nested case-control	United States
			4-<8	Nested case-control	United States
			8-<20	Nested case-control	United States
			>=20	Nested case-control	United States
Lewis, 1999, 627293	Diabetes Mellitus Mortality	Cumulative Arsenic Exposure (Males), Drinking Water, ppb-year	<1,000	Cohort (Retrospective)	United States
			1,000-4,999	Cohort (Retrospective)	United States
			>=5,000	Cohort (Retrospective)	United States
		Cumulative Arsenic Exposure (Females), Drinking Water, ppb-year	<1,000	Cohort (Retrospective)	United States
			1,000-4,999	Cohort (Retrospective)	United States
			>=5,000	Cohort (Retrospective)	United States
Pan, 2013, 2064256	Type 2 Diabetes	Arsenic in Drinking Water (Quartiles), ug/L	<=1.7	Case-control	Bangladesh
			1.8-15.5	Case-control	Bangladesh
			15.6-170.0	Case-control	Bangladesh
			>=170.1	Case-control	Bangladesh
Tseng, 2000, 15637	Diabetes Mellitus	Arsenic in Drinking Water, mg/L-year	<17	Cohort (Prospective)	Taiwan
			>=17	Cohort (Prospective)	Taiwan

(a) Ratio measures, drinking water, categorical exposure

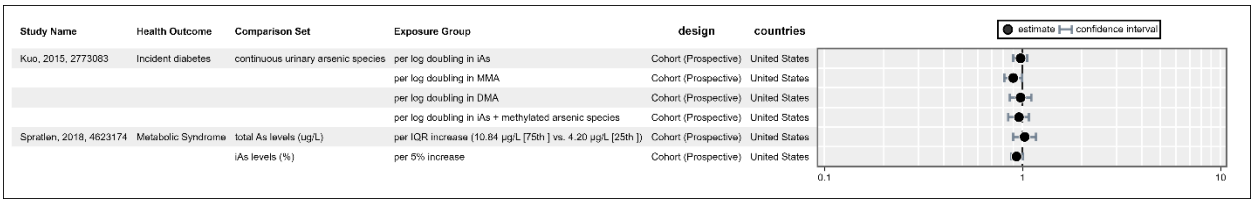


Study Name	Health Outcome	Comparison Set	Exposure Group	N	Exposure metric	design	countries
Ettinger, 2009, 627090	Impaired Glucose Tolerance	Blood Arsenic Concentration (Quartiles), ug/L	0.23-0.92	133	blood	Cohort (Prospective)	United States
			0.93-1.39	133	blood	Cohort (Prospective)	United States
			1.4-2.08	133	blood	Cohort (Prospective)	United States
			2.09-24.07	133	blood	Cohort (Prospective)	United States
		Hair Arsenic Concentration (Quartiles), ng/g	1.1-8.81	44	hair	Cohort (Prospective)	United States
			8.93-13.11	45	hair	Cohort (Prospective)	United States
			13.26-24.12	45	hair	Cohort (Prospective)	United States
			24.22-724.41	45	hair	Cohort (Prospective)	United States
Grau-Pérez, 2017, 3445362	Type 2 Diabetes	75th vs 25th Percentile, Plasma, ng/L	Total As (110.3 vs 63.8)	688	plasma	Case-control	United States
			iAs (63.1 vs 40.7)	688	plasma	Case-control	United States
			MMA (13.9 vs 4.2)	688	plasma	Case-control	United States
			DMA (30.1 vs 13)	688	plasma	Case-control	United States
		Tertiles, Plasma, ng/L	Tertile 1	86	plasma	Case-control	United States
			Tertile 2	98	plasma	Case-control	United States
			Tertile 3	75	plasma	Case-control	United States
Li, 2017, 4242758	diabetes	plasma arsenic tertiles	<0.389	184	plasma	Case-control	China
			0.389-0.915	184	plasma	Case-control	China
			>0.915	183	plasma	Case-control	China
Pan, 2013, 2064256	Type 2 Diabetes	Arsenic in Toenail Samples (Quartiles), ug/g	<=0.93		toenails	Case-control	Bangladesh
			0.94-2.12		toenails	Case-control	Bangladesh
			2.13-6.18		toenails	Case-control	Bangladesh
			>=6.19		toenails	Case-control	Bangladesh
Simić, 2017, 3800962	Type 2 Diabetes	Blood Arsenic Lowest vs Highest Quartile, ug/L	Q4 vs Q1		blood	Case-control	Norway
Yuan, 2018, 4241822	Diabetes	plasma arsenic quartile	Q1 (<1.19)	489	plasma	Nested case-control	China
			Q2 (1.19-1.80)	476	plasma	Nested case-control	China
			Q3 (1.80-3.25)	551	plasma	Nested case-control	China
			Q4 (>3.25)	562	plasma	Nested case-control	China
		plasma arsenic, 75th vs 25th percentiles	75th vs 25th percentile		plasma	Nested case-control	China

(b) Ratio measures, nonurinary biomarkers, categorical exposure



(c) Ratio measures, urine, categorical exposure



(d) Ratio measures, urine, continuous exposure

Figure 3-25. Case-control/Cohort epidemiologic studies examining the association between inorganic arsenic and diabetes (a) ratio measures, drinking water, categorical exposure; (b) ratio measures, other biomarker, categorical exposure; (c) ratio measures, urine, categorical exposure; (d) ratio measures, urine, continuous exposure (see interactive data graphic).

Case-control studies largely observed an association between iAs exposure in drinking water and increased diabetes risk. One prospective study, James et al. (2013), used geospatial mapping of drinking water arsenic concentrations to ascertain lifetime exposure levels (<150 µg/L) relative to diabetes prevalence in the San Luis Valley Diabetes Study participants in rural Colorado, a strong study design for temporal relevance of arsenic drinking water exposure. The authors concluded that risk of type 2 diabetes increased by 27% for each 15-µg/L increase in time-weighted average (TWA) residential iAs water concentration (HR=1.27; 95% CI: 1.02, 1.64). Kim et al. (2013) observed that arsenic exposure was associated with an increased OR (2.14; 95% CI: 1.19, 3.85) for developing type 2 diabetes when comparing the highest three exposure quartiles (4.6–36 µg/L; urinary iAs) to the lowest quartile in the United States. Pan et al. (2013b) reported an increased OR in the highest two quartiles of arsenic exposure (15.6–170 µg/L in drinking water, OR=3.07, 95% CI: 1.38, 6.85; ≥170.1 µg/L in drinking water, OR=4.51, 95% CI: 2.01, 10.09) compared with the lowest quartile of exposure in a Bangladeshi population. Kim et al. (2013) was based on a single

spot urine sample to determine arsenic concentration and therefore reflects exposure at one point in time, but groundwater inorganic arsenic is not expected to fluctuate substantially over time (Kim et al., 2013). In a population in Bangladesh, measurement of arsenic exposure occurred prior to diabetes development, with similar associations seen with both drinking water exposure (median 15.2 µg/L at baseline; 8.73 µg/L at follow-up) and toenail biomarker (Pan et al., 2013b). From another study in Bangladesh, Nizam et al. (2013) examined the metabolism of arsenic in diabetics (mean arsenic in drinking water: 85.1 µg/L) as compared with nondiabetics (mean arsenic in drinking water: 85.8 µg/L) and did not observe a significant difference in urinary arsenic metabolites between the groups.

Coronado-González et al. (2007) evaluated subjects from an arseniasis-endemic region from Coahuila, a northern state of Mexico with a high incidence of diabetes. The analysis by Coronado-González et al. (2007) identified a positive association for type 2 diabetes in participants with urinary arsenic concentrations 63.5–104 µg/g creatinine (OR = 2.16; 95% CI: 1.23, 3.79), and a three times greater risk for those with >100 µg/g creatinine (OR = 2.84; 95% CI: 1.64, 4.92); values not adjusted for creatinine presented similar results (data not shown).

Consistent findings were seen in other highly exposed areas, like Taiwan (Hsu et al., 2013), as well as lower-exposed areas, including the Northern Plains (Kuo et al., 2015) in the U.S. (median (IQR) urine concentration of inorganic arsenic plus methylated species: 10.2 (6.1–17.7) µg/L). In the U.S. (Kuo et al., 2015), higher iAs% and DMA% in urine, when MMA% decreased, was associated with diabetes incidence in the Strong Heart Study [HR (95% CI) of diabetes incidence per 5% increase in arsenic metabolism biomarkers: 1.00 (0.89–1.12) for iAs% and 1.07 (1.00–1.15)] for DMA%. Null results were observed in Utah, U.S. (Lewis et al., 1999).

Two studies based on data from multiple health surveys of the general adult population in Norway (Hansen et al., 2017; Simić et al., 2017) reported no associations between iAs and diabetes in this Norwegian population (median iAs = 0.05 µg/L in drinking water).

Cross-sectional studies

Thirty-two (*medium* and *high* confidence) cross-sectional studies (Zierold et al., 2004; Yang et al., 2017; Xiao et al., 2018; Velmurugan et al., 2018; Steinmaus et al., 2009; Rhee et al., 2013; Rahman and Axelson, 2001; Peng et al., 2015a; Park et al., 2015; Navas-Acien et al., 2008, 2009a; Mendez et al., 2016; Liu et al., 2016; Lin et al., 2014; Li et al., 2013a; Lampron-Goulet et al., 2017; Lai et al., 1994; Islam et al., 2012b; Huang et al., 2014; Gunduz et al., 2017; Gribble et al., 2012; Grau-Perez et al., 2018; Feseke et al., 2015; Feng et al., 2015; Drobná et al., 2013; Del Razo et al., 2011; Currier et al., 2014; Claus Henn et al., 2016; Chen et al., 2010c; Chen et al., 2011a; Adams et al., 2015) evaluated arsenic exposure in association with diabetes (see Figure 3-25). One of the oldest studies to identify a possible relationship between arsenic exposure and increased risk of diabetes was conducted by Lai et al. (1994). The study authors were interested in examining occurrence of diabetes related to arsenic exposure because this health outcome is closely related to vascular and peripheral artery disease (e.g., Blackfoot disease) that has been observed in high-exposure, arsenic-

endemic areas. More recent cross-sectional studies of populations across the world consistently report a positive relationship between arsenic exposure and diabetes (Lampron-Goulet et al., 2017; Currier et al., 2014; Feng et al., 2015; Feseke et al., 2015; Drobná et al., 2013; Rhee et al., 2013; Islam et al., 2012b; Del Razo et al., 2011; Gribble et al., 2012; Lin et al., 2014; Yang et al., 2017; Grau-Perez et al., 2018; Velmurugan et al., 2018; Gunduz et al., 2017; Xiao et al., 2018; Zierold et al., 2004; Park et al., 2015). These studies evaluated associations with arsenic concentration in drinking water, cumulative arsenic exposure measures, or internal biomarkers of exposure (primarily urine). Generally, the exposure definition either involved a single biomarker measurement or a metric reflecting the combination of data from both biomarker and drinking water samples. In the few studies that looked at cumulative exposure, water consumption data and water arsenic concentration was often the only measure(s) used (e.g., weighted average (µg/L) as a function of drinking durations and well arsenic concentrations). Although the relevance of exposure measured cross-sectionally to the development of diabetes is less certain, the results of these studies were largely consistent across exposure measure types and are consistent with the findings of the cohort and case-control studies.

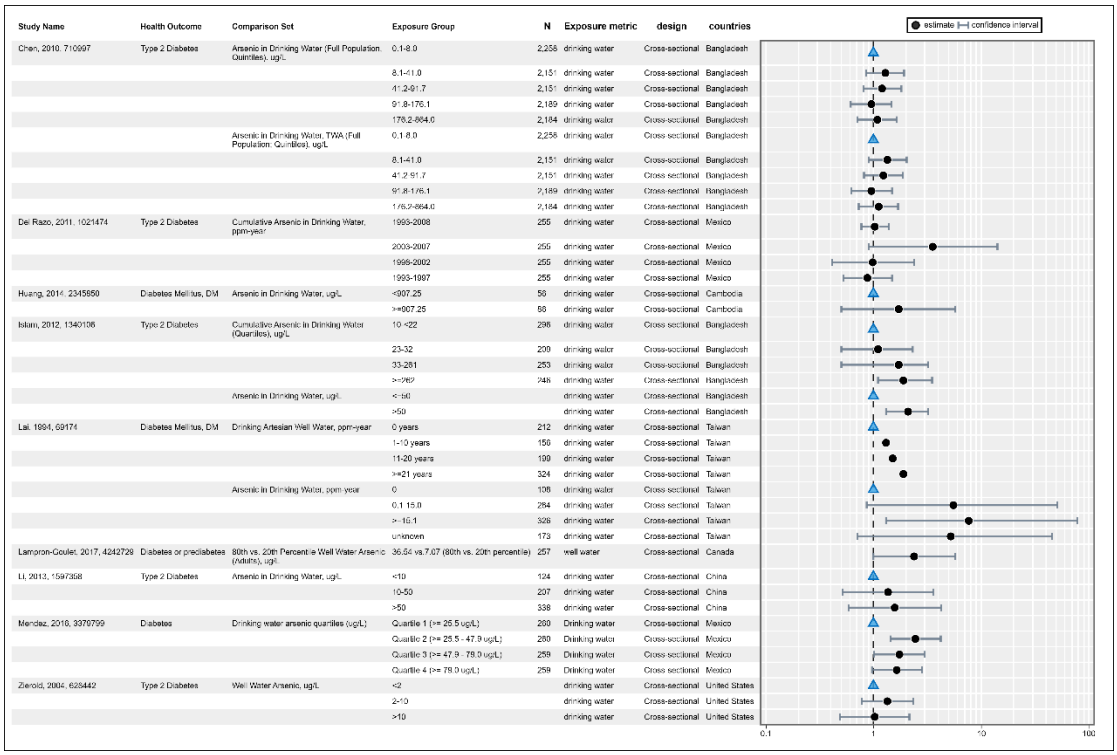
Currier et al. (2014) examined associations between arsenic species (including methylarsonate [MAIII) and dimethylarsinite [DMAIII]) in exfoliated urothelial cell (an alternative to the measures of iAs in urine) and the prevalence of diabetes among residents of Chihuahua, Mexico (mean sum of As species in urine: 109.7 ng As/specific gravity unit). They found a positive OR for the sum of arsenic species (1.24; 95% CI: 0.91, 1.68) and positive, significant ORs for iAs III, MA III, iAs(III+V), DMA/MA, and DMA/iAs but not for other species, suggesting that trivalent iAs species may be responsible for associations between iAs exposure and diabetes. Additional studies by these authors further observed a significant increase in OR (i.e., 1.13 95% CI: 1.05–1.22) per 10 µg/L increase in drinking water in an arsenicosis-endemic area of Mexico but did not find an increase when evaluating cumulative exposures by ppm-years (Del Razo et al., 2011; Mendez et al., 2016). The authors suggest that this was likely due to changes in levels of iAs in drinking water supplies in recent years as a result of government interventions to reduce exposure. Drobná et al. (2013) conducted genotyping that focused on six polymorphic sites of AS3MT and reported that subjects with a variant type M287T and G4965C polymorphisms had higher levels of DMA(III) and were more susceptible to developing diabetes, providing support for the role of arsenic methylation and diabetes risk.

Additional cross-sectional studies provided further support for the association between iAs and diabetes risk. For example, Gribble et al. (2012) reported on a large American Indian population residing in the U.S. (Strong Heart Study, n ~ 4,000) with increasing adjusted prevalence ratios for diabetes in relation to quartiles of urinary arsenic concentrations ranging from <7.9 to >24.2 µg/L. Also in the U.S., using NHANES data, urinary arsenic was associated with increased prevalence of type 2 diabetes (Navas-Acien et al., 2009a; Navas-Acien et al., 2008); and Adams et al. (2015) observed an association between urinary arsenic (mean: 18.7 µg/L) and type 2 diabetes in

older Hispanic adults living in southern New Mexico. However, Steinmaus et al. (2009) saw no increased risk of diabetes with arsenic exposure (median: 7.6 μg/L) in NHANES adults; and Peng et al. (2015a), when examining urinary arsenic (median: 7.01 μg/L) and insulin resistance in NHANES adolescents, did not observe an association. A dose-response gradient was observed within a number, but not all, studies (Xiao et al., 2018; Velmurugan et al., 2018; Rhee et al., 2013; Navas-Acien et al., 2008; Li et al., 2013a; Lai et al., 1994; Islam et al., 2012b; Gribble et al., 2012; Grau-Perez et al., 2018; Feseke et al., 2015; Feng et al., 2015; Chen et al., 2011a).

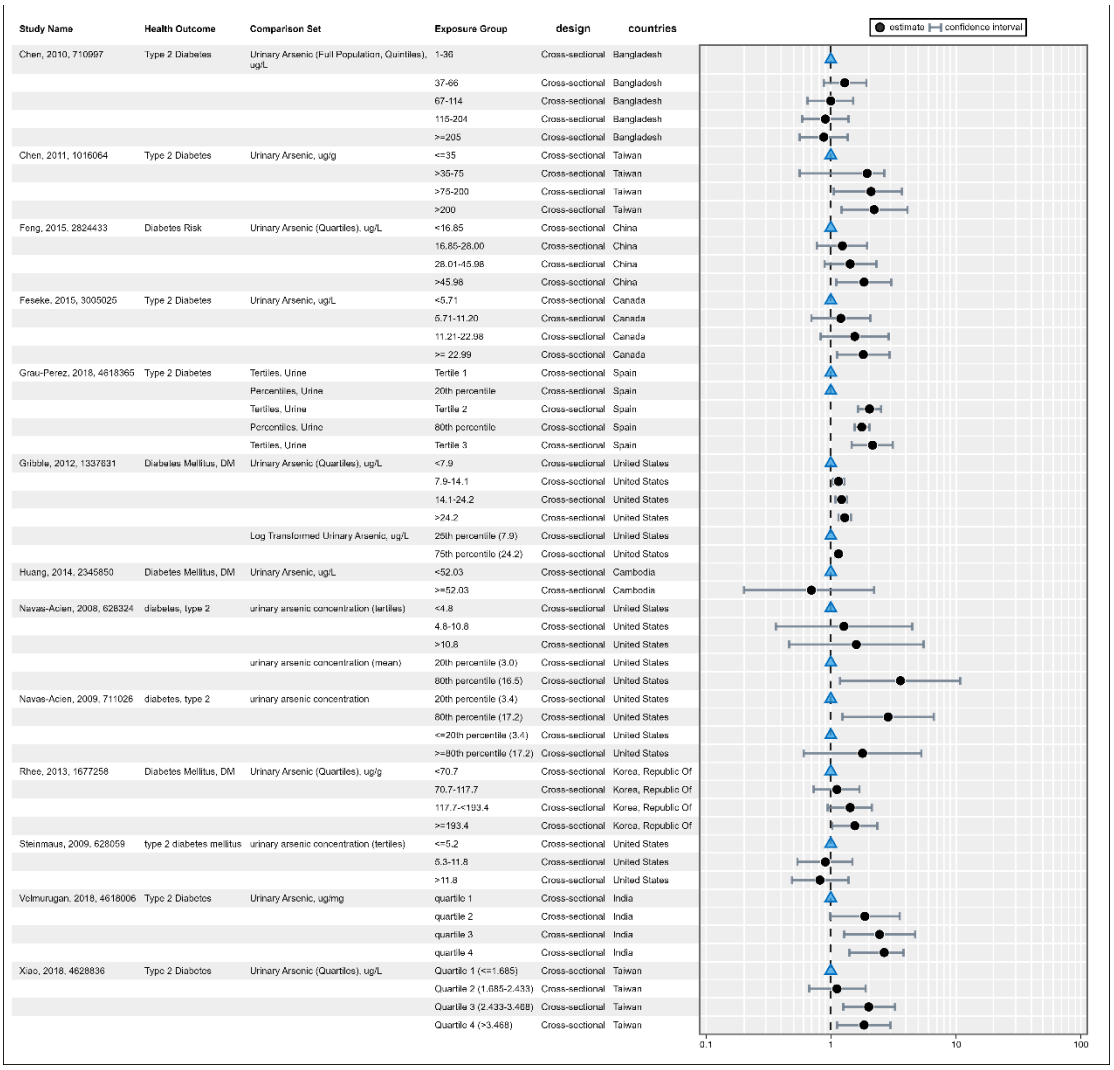
In Korea, Rhee et al. (2013) reported a statistically significant OR in the highest quartile of arsenic exposure (≥193.4 μg/g creatinine urinary total arsenic; OR = 1.56; 95% CI: 1.03, 2.36) compared with the lowest exposure group (<80.7 μg/g creatinine); ORs exhibited a positive linear trend when comparing quartiles. In KHANES (the Korean National Health and Nutrition Examination Survey), Kim and Lee (2011) observed an association between urinary arsenic concentration and diabetes in adults. Lin et al. (2014) examined the association between urinary arsenic and insulin resistance in obese children (mean total As concentration: 23.01 μg/L) and adolescents using the homeostasis model assessment of insulin resistance (HOMA-IR) index and found that for all students in the summary model, HOMA-IR levels were significantly increased with increases in total arsenic concentrations.

Grau-Perez et al. (2018) examined the association of inorganic arsenic exposure and polymorphisms on diabetes-related genes in a representative sample from a population in Valladolid, Spain. The mean total arsenic in the study was 66.0 μg/g. The authors observed an OR (95% confidence interval) for diabetes when comparing the highest with the lowest tertile of total arsenic as follows: 1.76 (1.01, 3.09) and 2.14 (1.47, 3.11) (respectively, pre and post adjustments for arsenobetaine an organoarsenic found in seafood). A cross-sectional study in Taiwan reported an association between arsenic exposure and diabetes, which showed an increasing trend [OR(95% CI): 2.08(1.05–3.69) and 2.22(1.21–4.09) for urinary arsenic levels of >75–200 and >200 $\mu g/g^{-1}$ creatinine, respectively, compared with reference <35 $\mu g/g^{-1}$ creatinine](Chen et al., 2011a). In Cambodia, drinking water with arsenic levels above the median (907.25 μg/L) was associated with a statistically significant increase of diabetes in adults (Huang et al., 2014). In Bangladesh, Chen et al. (2010c) observed no association between well water or urinary arsenic and HbA1c level in the HEALS cohort; and Rahman and Axelson (2001) examined arsenic levels in drinking water (drinking water arsenic concentration range: nondetectable–2,040 μg/L) with presence of skin lesions as indicator of exposure and found an association between exposure to arsenic and glucosuria. In China, Li et al. (2013a) did not observe an association between arsenic exposure (range of arsenic in wells ranged from 0–760 μg/L) and type 2 diabetes.



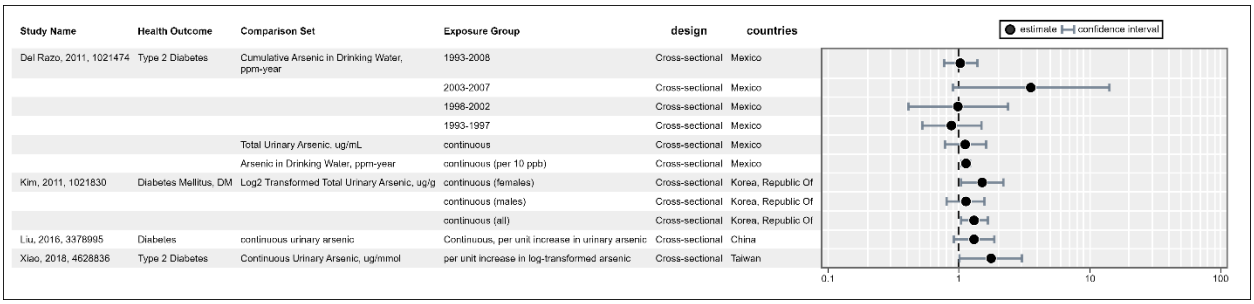
Study Name	Health Outcome	Comparison Set	Exposure Group	N	Exposure metric	design	countries
Chen, 2010, 710997	Type 2 Diabetes	Arsenic in Drinking Water (Full Population Quintiles), ug/L	0.1-8.0	2,258	drinking water	Cross-sectional	Bangladesh
			8.1-41.0	2,151	drinking water	Cross-sectional	Bangladesh
			41.2-91.7	2,151	drinking water	Cross-sectional	Bangladesh
			91.8-176.1	2,189	drinking water	Cross-sectional	Bangladesh
			176.2-864.0	2,184	drinking water	Cross-sectional	Bangladesh
		Arsenic in Drinking Water, TWA (Full Population Quintiles), ug/L	0.1-8.0	2,258	drinking water	Cross-sectional	Bangladesh
			8.1-41.0	2,151	drinking water	Cross-sectional	Bangladesh
			41.2-91.7	2,151	drinking water	Cross-sectional	Bangladesh
			91.8-176.1	2,189	drinking water	Cross-sectional	Bangladesh
			176.2-864.0	2,184	drinking water	Cross-sectional	Bangladesh
Del Razo, 2011, 1021474	Type 2 Diabetes	Cumulative Arsenic in Drinking Water, ppm-year	1993-2008	255	drinking water	Cross-sectional	Mexico
			2003-2007	255	drinking water	Cross-sectional	Mexico
			1998-2002	255	drinking water	Cross-sectional	Mexico
			1993-1997	255	drinking water	Cross-sectional	Mexico
Huang, 2014, 2345850	Diabetes Mellitus, DM	Arsenic in Drinking Water, ug/L	<907.25	56	drinking water	Cross-sectional	Cambodia
			>=907.25	56	drinking water	Cross-sectional	Cambodia
Islam, 2012, 1340106	Type 2 Diabetes	Cumulative Arsenic in Drinking Water (Quartiles), ug/L	10 <22	296	drinking water	Cross-sectional	Bangladesh
			23-32	209	drinking water	Cross-sectional	Bangladesh
			33-281	253	drinking water	Cross-sectional	Bangladesh
			>=282	248	drinking water	Cross-sectional	Bangladesh
		Arsenic in Drinking Water, ug/L	<=50		drinking water	Cross-sectional	Bangladesh
			>50		drinking water	Cross-sectional	Bangladesh
Lai, 1994, 69174	Diabetes Mellitus, DM	Drinking Artesian Well Water, ppm-year	0 years	212	drinking water	Cross-sectional	Taiwan
			1-10 years	156	drinking water	Cross-sectional	Taiwan
			11-20 years	109	drinking water	Cross-sectional	Taiwan
			>=21 years	324	drinking water	Cross-sectional	Taiwan
		Arsenic in Drinking Water, ppm-year	0	106	drinking water	Cross-sectional	Taiwan
			0.1-15.0	264	drinking water	Cross-sectional	Taiwan
			>=15.1	326	drinking water	Cross-sectional	Taiwan
			unknown	173	drinking water	Cross-sectional	Taiwan
Lampron-Goulet, 2017, 4242729	Diabetes or prediabetes	80th vs. 20th Percentile Well Water Arsenic (Adults), ug/l.	36.54 vs.7.07 (80th vs. 20th percentile)	257	well water	Cross-sectional	Canada
Li, 2013, 1597368	Type 2 Diabetes	Arsenic in Drinking Water, ug/L	<10	124	drinking water	Cross-sectional	China
			10-50	207	drinking water	Cross-sectional	China
			>50	338	drinking water	Cross-sectional	China
Mendez, 2016, 3370799	Diabetes	Drinking water arsenic quartiles (ug/L)	Quartile 1 (>= 25.5 ug/L)	260	Drinking water	Cross-sectional	Mexico
			Quartile 2 (>= 25.5 - 47.9 ug/L)	260	Drinking water	Cross-sectional	Mexico
			Quartile 3 (>= 47.9 - 78.9 ug/L)	259	Drinking water	Cross-sectional	Mexico
			Quartile 4 (>= 78.9 ug/L)	259	Drinking water	Cross-sectional	Mexico
Zierold, 2004, 625442	Type 2 Diabetes	Well Water Arsenic, ug/L	<2		drinking water	Cross-sectional	United States
			2-10		drinking water	Cross-sectional	United States
			>10		drinking water	Cross-sectional	United States

(a) Ratio measures, drinking water, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	design	countries
Chen, 2010, 710997	Type 2 Diabetes	Urinary Arsenic (Full Population, Quintiles), ug/L	1-36	Cross-sectional	Bangladesh
			37-66	Cross-sectional	Bangladesh
			67-114	Cross-sectional	Bangladesh
			115-204	Cross-sectional	Bangladesh
			>=205	Cross-sectional	Bangladesh
Chen, 2011, 1016064	Type 2 Diabetes	Urinary Arsenic, ug/g	<=35	Cross-sectional	Taiwan
			>35-75	Cross-sectional	Taiwan
			>75-200	Cross-sectional	Taiwan
			>200	Cross-sectional	Taiwan
Feng, 2015, 2824433	Diabetes Risk	Urinary Arsenic (Quartiles), ug/L	<16.85	Cross-sectional	China
			16.85-28.00	Cross-sectional	China
			28.01-45.98	Cross-sectional	China
			>45.98	Cross-sectional	China
Feseke, 2015, 3005025	Type 2 Diabetes	Urinary Arsenic, ug/L	<5.71	Cross-sectional	Canada
			5.71-11.20	Cross-sectional	Canada
			11.21-22.98	Cross-sectional	Canada
			>= 22.99	Cross-sectional	Canada
Grau-Perez, 2018, 4618365	Type 2 Diabetes	Tertiles, Urine	Tertile 1	Cross-sectional	Spain
		Percentiles, Urine	20th percentile	Cross-sectional	Spain
		Tertiles, Urine	Tertile 2	Cross-sectional	Spain
		Percentiles, Urine	80th percentile	Cross-sectional	Spain
		Tertiles, Urine	Tertile 3	Cross-sectional	Spain
Gribble, 2012, 1337831	Diabetes Mellitus, DM	Urinary Arsenic (Quartiles), ug/L	<7.9	Cross-sectional	United States
			7.9-14.1	Cross-sectional	United States
			14.1-24.2	Cross-sectional	United States
			>24.2	Cross-sectional	United States
		Log Transformed Urinary Arsenic, ug/L	25th percentile (7.9)	Cross-sectional	United States
			75th percentile (24.2)	Cross-sectional	United States
Huang, 2014, 2345850	Diabetes Mellitus, DM	Urinary Arsenic, ug/L	<52.03	Cross-sectional	Cambodia
			>=52.03	Cross-sectional	Cambodia
Navas-Acien, 2008, 628324	diabetes, type 2	urinary arsenic concentration (tertiles)	<4.8	Cross-sectional	United States
			4.8-10.8	Cross-sectional	United States
			>10.8	Cross-sectional	United States
		urinary arsenic concentration (mean)	20th percentile (3.0)	Cross-sectional	United States
			80th percentile (16.5)	Cross-sectional	United States
Navas-Acien, 2009, 711026	diabetes, type 2	urinary arsenic concentration	20th percentile (3.4)	Cross-sectional	United States
			80th percentile (17.2)	Cross-sectional	United States
			<=20th percentile (3.4)	Cross-sectional	United States
			>=80th percentile (17.2)	Cross-sectional	United States
Rhee, 2013, 1677258	Diabetes Mellitus, DM	Urinary Arsenic (Quartiles), ug/g	<70.7	Cross-sectional	Korea, Republic Of
			70.7-117.7	Cross-sectional	Korea, Republic Of
			117.7-<193.4	Cross-sectional	Korea, Republic Of
			>=193.4	Cross-sectional	Korea, Republic Of
Steinmaus, 2009, 628059	type 2 diabetes mellitus	urinary arsenic concentration (tertiles)	<=5.2	Cross-sectional	United States
			5.3-11.8	Cross-sectional	United States
			>11.8	Cross-sectional	United States
Velmurugan, 2018, 4618006	Type 2 Diabetes	Urinary Arsenic, ug/mg	quartile 1	Cross-sectional	India
			quartile 2	Cross-sectional	India
			quartile 3	Cross-sectional	India
			quartile 4	Cross-sectional	India
Xiao, 2018, 4628836	Type 2 Diabetes	Urinary Arsenic (Quartiles), ug/L	Quartile 1 (<=1.685)	Cross-sectional	Taiwan
			Quartile 2 (1.685-2.433)	Cross-sectional	Taiwan
			Quartile 3 (2.433-3.468)	Cross-sectional	Taiwan
			Quartile 4 (>3.468)	Cross-sectional	Taiwan

(b) Ratio measures, urine, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	design	countries
Del Razo, 2011, 1021474	Type 2 Diabetes	Cumulative Arsenic in Drinking Water, ppm-year	1993-2008	Cross-sectional	Mexico
			2003-2007	Cross-sectional	Mexico
			1998-2002	Cross-sectional	Mexico
			1993-1997	Cross-sectional	Mexico
		Total Urinary Arsenic, ug/mL	continuous	Cross-sectional	Mexico
		Arsenic in Drinking Water, ppm-year	continuous (per 10 ppb)	Cross-sectional	Mexico
Kim, 2011, 1021830	Diabetes Mellitus, DM	Log2 Transformed Total Urinary Arsenic, ug/g	continuous (females)	Cross-sectional	Korea, Republic Of
			continuous (males)	Cross-sectional	Korea, Republic Of
			continuous (all)	Cross-sectional	Korea, Republic Of
Liu, 2016, 3378995	Diabetes	continuous urinary arsenic	Continuous, per unit increase in urinary arsenic	Cross-sectional	China
Xiao, 2018, 4628836	Type 2 Diabetes	Continuous Urinary Arsenic, ug/mmol	per unit increase in log-transformed arsenic	Cross-sectional	Taiwan

(c) Ratio measures, urine, continuous exposure

Figure 3-26. Cross-sectional epidemiologic studies examining the association between arsenic and diabetes (a) ratio measures, drinking water, categorical exposure; (b) ratio measures, urine, categorical exposure; (c) ratio measures, urine, continuous exposure (see interactive data graphic).

Other: Type 1 diabetes and gestational diabetes

While the literature base largely examines type 2 diabetes, studies also examined type 1 diabetes (Grau-Pérez et al., 2017) and gestational diabetes (Shapiro et al., 2015; Peng et al., 2015b; Farzan et al., 2016; Ettinger et al., 2009; Claus Henn et al., 2016). These studies were largely consistent in demonstrating a positive association between arsenic exposure and incidence of type 1 diabetes mellitus or gestational diabetes.

In the type 1 diabetes study, Grau-Pérez et al. (2017) found folate intake to be a modifier of iAs metabolism associated with type 1 diabetes. The study examined the association of dietary intake of folate and vitamin B12 on iAs metabolism (specifically, one carbon metabolism) on the odds ratios of diabetes in youth (<20 years old). The results showed that ΣiAs was not associated with type 1 diabetes. However, the methylarsonite (MMA)% OR of type 1 diabetes showed an association between arsenic metabolism and type 1 diabetes (OR 1.80 (1.25–2.58) and 0.98 (0.70–1.38) for participants with plasma folate levels above and below the median (20.2 μg/L) (P for interaction = 0.02), respectively), indicating nutrition, in this case folate intake, may play a risk modifying role in iAs diabetes risk (Grau-Pérez et al., 2017; Grau-Pérez et al., 2017). Peng et al. (2015b) recruited participants from a maternity and childcare hospital in China and measured arsenic levels in newborn meconium samples. They reported positive dose-dependent trends between arsenic in the samples and incidence of maternal gestational diabetes. The trend for arsenic was significant for 2nd (OR = 3.28; 95% CI: 1.24, 8.71); 3rd (OR = 3.35; 95% CI: 1.28, 8.75); and 4th (OR = 5.25; 95% CI: 1.99, 13.86) quartiles of arsenic. In rural Oklahoma, U.S., inverse associations between arsenic (median (IQR) maternal and umbilical cord blood concentration: 1.4 (0.97 - 2.3) and 2.4 (1.8 - 3.3) μg/L, respectively) and all birth outcomes (birth weight, gestational age, birth weight for gestational age, head circumference) were observed to be stronger among women with impaired glucose tolerance (Claus Henn et al., 2016).

Mechanistic Observations and Biological Plausibility

The etiology of arsenic-associated diabetes is not clearly understood, but arsenic is hypothesized to interfere with pancreatic beta-cell function, insulin/glucose uptake and transport, insulin signaling pathways, and gluconeogenesis [Reviewed in (Díaz-Villaseñor et al., 2007)]. Other nonspecific effects include oxidative stress and interruption of calcium signaling. Details on these and other modes of action for arsenic are described in detail in Appendix A of the iAs Protocol. In one relatively recent review, Martin et al. (2017) identified four major mechanisms underlying arsenic-associated diabetes. These include: (1) inhibition of insulin dependent glucose uptake; (2) production of ROS leading to β-cell damage and chronic inflammation; (3) β-cell dysfunction due to increased ROS production; and (4) stimulation of glucogenesis. However, the authors noted the importance of the need to develop models that better assess the low-dose effects of arsenic on glucose homeostasis given that the evidence for mechanisms of arsenic-induced diabetes are based on studies that evaluated elevated arsenic levels in rodents and in vitro model systems that are not

physiologically relevant to human environmental arsenic exposures. Nonetheless, these data could provide useful information on potential disruption of cellular homeostatic pathways associated with arsenic exposure.

Along with the epidemiological evidence from populations exposed to inorganic arsenic, in vivo and in vitro studies have shown that exposure to iAs can produce effects that correspond to insulin resistance and diabetogenic phenotypes. As discussed in Section 3.2.2 inorganic arsenic may induce diabetogenic effects through a variety of pathways including inhibition of insulin-dependent glucose uptake, interference with insulin signaling pathways, pancreatic beta-cell damage or dysfunction, and stimulation of hepatic glucogenesis [Reviewed in (Díaz-Villaseñor et al., 2007) and (Shakya et al., 2023)]. Other nonspecific effects include oxidative stress and interruption of calcium signaling as well as modulation of gene expression of genes involved in insulin signaling and adipocyte differentiation (Shakya et al., 2023) (see the iAs Protocol (link provided in Appendix A) for details on possible modes of action). As an example, Liu et al. (2014) exposed wild-type (C57BKS/J db/m) and C57BKS/Lepr^{db} mice exposed to 3 mg/L sodium arsenite for 16 weeks. C57BKS/Lepr^{db} are an in vivo model for diabetes. The authors showed that arsenic caused pancreatic beta-cell dysfunction and increased gluconeogenesis and oxidative damages in the livers of wild-type mice. Further, arsenic worsened glucose tolerance in the C57BKS/Lepr^{db} mice, suggesting that iAs exposure can cause prediabetic effects in normal individuals and worsen diabetic effects in diabetes individuals. Arsenic also caused a dose-dependent decrease in glucose uptake and insulin response in murine 3T3-L1 adipocytes and C2C12 myotubes exposed to 0, 0.5, 1, or 2 μM sodium arsenite for 8 weeks in vitro (Divya et al., 2015). These data provide evidence for the biological plausibility of inorganic arsenic to disrupt glucose-insulin homeostasis and induce diabetogenic effects.

Risk Modifiers

A review of the epidemiological studies discussed in this section, along with studies identified from a targeted literature search on modifying factors (see Section 3.10 of iAs Protocol) identified in Table 3-4, suggest that the following factors increase the risk of arsenic-associated diabetes:

- **Genetic variation:** The evidence suggests that individuals with certain polymorphisms that alter the metabolism of inorganic arsenic independently of excretion or absorption (e.g., GST, AS3MT) or increase the organ or cellular toxicity of inorganic arsenic might have an increased risk for diabetes from arsenic exposure. Specifically, polymorphisms in GSTO1, AS3MT, NOTCH2, and Calpain-10 have been identified as being associated with susceptibility to diabetes in arsenic-exposed populations. Polymorphisms in five diabetes-related genes (IL8RA, TXN, NR3C2, COX5A and GCLC) also showed a suggestive differential association of urine total arsenic with diabetes prevalence.

- **Methylation capacity:** The evidence suggests that decreased methylation capacity increases insulin sensitivity and may increase risk of diabetes. Contrary to what has been

observed for other health outcomes, lower MMA% and higher DMA% in urine has been associated with increased risk of diabetes-related outcomes in populations from Taiwan, Mexico, and the U.S. (Chen et al., 2012a; Currier et al., 2014; Grau-Pérez et al., 2017).

- **Nutrition:** The evidence suggests that individuals with high BMI may be at increased risk of diabetes. Increased BMI and smoking status have been examined as factors in multivariate analyses of diabetes risk and arsenic exposure and might have potential additive affects. Vitamin B intake and folate levels may also increase risk of diabetes.

- **Smoking:** The evidence suggests that smokers may have an increased risk for diabetes from arsenic exposure. Evidence indicates a synergistic effect between arsenic and smoking from one study. There was a significant interaction between smoking and arsenic exposure for past or current male smokers exposed to higher levels of arsenic in drinking water (≥15.5 µg/L) compared with nonsmokers exposed to lower levels (<15.5 µg/L) (Pan et al., 2013b). Smoking history data were only available in men.

Table 3-4. Risk modifiers for diabetes from selected epidemiologic studies

Risk modifiers	References	Finding	Population, exposure level
Genetic variation	Chen et al. (2012a) Drobná et al. (2013)	GSTO1, AS3MT polymorphisms can affect arsenic methylation status.	Taiwan, 700–930 mg/L-yr, range (water); Mexico 43 µg/L, mean (water)
	Pan et al. (2013a)	NOTCH2 polymorphism increased susceptibility to diabetes.	Bangladesh, ≤1.7–≥170.1 µg/L, range (water)
	Díaz-Villaseñor et al. (2013)	Calpain-10 polymorphism can impair pancreatic beta-cell function and insulin sensitivity.	Mexico, 2.8–131.5 µg/L, range (water)
	Grau-Perez et al. (2018)	The analysis of polymorphisms in five diabetes-related genes (IL8RA, TXN, NR3C2, COX5A and GCLC) showed a suggestive differential association of urine total arsenic with diabetes prevalence.	Spain, geometric mean 66.0 µg/g total urinary arsenic
Methylation	Chen et al. (2012a)	Insulin sensitivity significantly increased at low methylation levels.	Taiwan, 700–930 mg/L-yr, range (water)
	Currier et al. (2014)	High DMA/MA ratio in urine may be a risk factor for diabetes.	Mexico, 55.2 µg/L, mean (water)
	Grau-Perez et al. (2017)	Lower MMA% associated with increased insulin resistance	United States, <50 µg/L (water)
Nutrition	Su et al. (2012) Pan et al. (2013b)	BMI can affect methylation capacity and risk of diabetes; potential additive effect of high BMI and arsenic exposure (increased OR in overweight/obese individuals).	Taiwan, ND–4 µg/L, range (water); Bangladesh, ≤1.7–≥170.1 µg/L, range (water)

Risk modifiers	References	Finding	Population, exposure level
	Grau-Perez et al. (2017)	Arsenic metabolism with HOMA2-IR results differed among study participants according to vitamin B intake and AS3MT genetic variant	USA, American Indian Population, 5.9 µg/L total urinary arsenic
	Grau-Pérez et al. (2017)	Folate levels at or below median levels increased association between arsenic metabolism and type 1 diabetes due to increase %MMA	USA, American Indian Population, 5.9 µg/L total urinary arsenic
Smoking	Pan et al. (2013b)	Increased OR in men who smoke. Smoking history only available in men.	Bangladesh, ≤1.7–≥170.1 µg/L, range (water)

Evidence Judgment

The currently available human evidence is considered *robust* and the **evidence demonstrates** that iAs causes type 2 diabetes in humans (see Table 3-5) given sufficient exposure conditions.[20] This conclusion is based on studies of humans that assessed oral exposure to arsenic from contaminated drinking water. Diabetes diagnoses were generally based on glucose measurements, use of diabetes medication, or self-reported diagnoses with medical record verification. Study subjects included populations across three continents with different ethnic backgrounds; from arsenic-endemic areas (e.g., Bangladesh, Taiwan; >100 µg/L arsenic in drinking water) and those from geographical areas with comparatively lower levels of arsenic exposure (e.g., Denmark, United States; <100 µg/L arsenic in drinking water and including <20 µg/L).

A strong evidence base demonstrating arsenic exposure causes type 2 diabetes in humans comes from consistency across different study designs, cohort, case-control studies, and cross-sectional, which were largely consistent in demonstrating a positive association between arsenic exposure and incidence of type 2 diabetes and diabetes-related mortality. Trivalent arsenic species may also be responsible for associations between chronic iAs exposure and diabetes. A *dose-response gradient* was observed in many studies; several studies reported a strong exposure response gradient with hazard ratios usually around 2 when compared with those in lowest exposure category, often ≤10 µg/L, and a temporal relationship was evident in several prospective cohort studies in which prolonged arsenic exposure was associated with diabetes. There is *coherence* with type 1 and gestational diabetes findings. Studies also highlighted differences in the association between iAs exposure and diabetes for susceptible populations, such as genetic variation (e.g., individuals that carry polymorphisms in AS3MT gene); nutritional status; smoking status and methylation capacity.

[20]The term, "sufficient exposure conditions," is discussed and defined for the identified health effects in the dose-response analysis in Section 4.

Overall, the currently available epidemiologic **evidence demonstrates** that iAs causes type 2 diabetes in humans given sufficient exposure conditions. This conclusion is based on both higher and lower exposure scenarios, with studies of humans that assessed exposure levels much lower than 100 μg/L (<20 μg/L). (Supplemental figures of results from studies documenting adverse effects from exposure to inorganic arsenic in drinking water at concentrations less than or equal to 100 μg/L, as described in 1.6.3, are available in Appendix B.5.). This conclusion is based on a large set of case-control, cohort and cross-sectional studies that consistently reported associations with diabetes in populations exposed to iAs contaminated water ranging from ≤1.7 mg/L (range in water) to 930 mg/L-yr, (range water) exposure and, therefore, is considered for dose-response analysis (see Section 4.3.8).

Table 3-5. Evidence profile table for epidemiological evidence on iAs and type 2 diabetes

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
Studies	**Summary of key findings**	**Factors that increase certainty**	**Factors that decrease certainty**	**Evidence synthesis judgment(s)**
57 *medium* or *high* confidence studies	Generally consistent, positive associations with T2D across diverse populations and study designs in both higher and lower exposure scenarios. Some evidence for exposure-dependent changes within and across studies with well-characterized exposures, long duration exposures with sufficient follow-up for latency.	• Studies are *medium* or *high* confidence. • *Consistency* – of strong positive associations in populations across three continents, primarily at relatively low exposures to iAs in drinking water (<100 μg/L) *Dose-response gradient* – observed across many studies. • *Large* or *concerning magnitude* of effect-observed in some studies (e.g., ratio measures >2–>3) • *Coherence* – with type 1 diabetes and gestational diabetes findings	• No factors noted.	⊕⊕⊕ *Robust*

3.2.3. Fetal, Newborn, and Infant Health Outcomes

Database Overview

The NRC identified early life as a potential critical window of susceptibility to toxic effects from arsenic exposure and concluded that low-to-moderate levels of inorganic arsenic are associated with pregnancy and birth outcomes based on evidence from human studies (NRC, 2013). As a result, evaluation of fetal, newborn, and infant health outcomes is under consideration for dose-response analysis in the IRIS Toxicological Review. On the basis of the analysis of epidemiological evidence using the methods described in the protocol (link provided in Appendix A), the strength of evidence judgment for a causal association was considered "moderate." *Moderate* evidence from humans leads to an evidence integration conclusion of **evidence indicates (likely)** (U.S. EPA, 2022). This section summarizes the review of the *moderate* evidence supporting a conclusion that the currently available evidence indicates that iAs likely causes fetal, newborn, and infant health outcomes in humans.

A systematic literature search identified 104 epidemiological studies that evaluated the association between exposure to inorganic arsenic (iAs) and fetal, newborn, and infant health outcomes. Citations of studies broken down by confidence level, type of outcome, and studies identified in the 2022 literature update can be accessed via the interactive HAWC literature tag-tree visual presented in Figure 3-27.

These publications underwent study evaluation, and 69 studies were considered *medium* or *high* confidence while 23 were considered *low* or *uninformative*. Twelve studies identified in the 2022 update were not considered further due to lack of hazard or dose-response utility (see Section 1.6.1). This section focuses on the medium and high confidence studies. The study evaluations of the epidemiologic studies are summarized in HAWC.

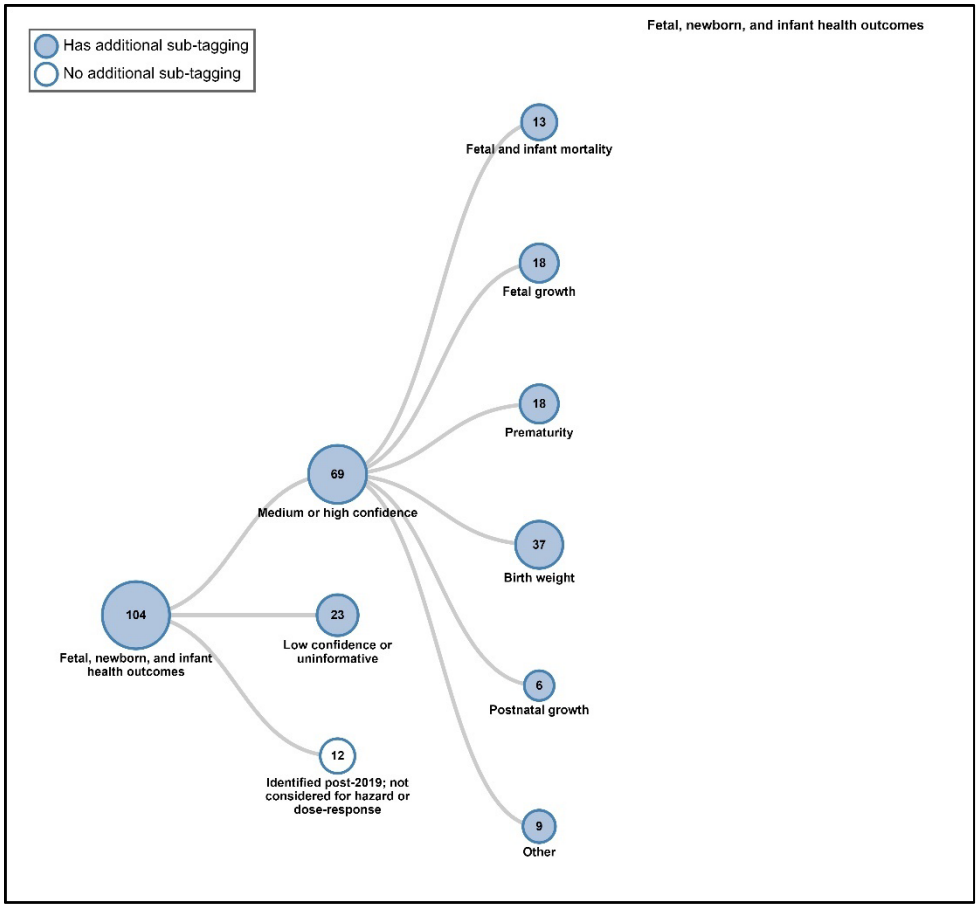


Figure 3-27. Literature tree of epidemiological studies assessing fetal, newborn, and infant health outcomes (see interactive version in HAWC).

This section presents a review of the evidence for an association between iAs exposure and fetal, newborn, and infant health effects over a range of environmental concentrations in Bangladesh, India, China, the United States, and other countries. Specific outcomes characterized in this section include fetal and infant loss (stillbirth and spontaneous abortion), fetal growth (e.g., head and chest circumference measured in utero or at time of birth), prematurity, birth weight, and growth (e.g., height-for-age, weight-for-age) in the first 10 years of life.[21] The strongest evidence characterizing the relationship between iAs exposure and fetal loss, infant mortality, prematurity, and other birth outcomes from prospective and cross-sectional studies conducted in Bangladesh and India, where iAs levels in drinking water wells commonly exceeded 200 µg/L. It should be noted that many of these cross-sectional studies included populations that had been highly exposed to arsenic for more than 5–10 years [e.g., (Ahmad et al., 2001; Milton et al., 2005)], which provides increased confidence with regard to temporality compared with typical cross-sectional study scenarios. Ecological studies (with long well-defined exposure periods, limited population

[21]Neurodevelopmental outcomes are discussed in Section 3.2.4.

migration, large sample sizes, and use of extensive group-level covariates in the analysis) also provide evidence to support an association between iAs exposure >100 µg/L and fetal and infant mortality. There is also evidence for iAs-associated effects at lower levels of arsenic exposure (e.g., <50 µg/L in drinking water) from cohort and cross-sectional studies on fetal, newborn, and infant health outcomes in the United States, Chile, and China [e.g., (Wang et al., 2022a; Mcdermott et al., 2014; Hopenhayn et al., 2003; Claus Henn et al., 2016; Almberg et al., 2017)].

Finally, this section summarizes mechanistic observations and also discusses how an association between iAs and fetal, newborn, and infant health outcomes might be influenced by potential risk modifiers (e.g., polymorphisms, nutrition, methylation capacity, sex).

Evidence from Epidemiological Studies

This section summarizes the epidemiological studies that evaluated an association between iAs exposure and fetal or infant mortality, fetal growth, prematurity, birth weight, or postnatal growth. Investigators assessed arsenic exposure by measuring levels in drinking water, air, and soil or by using internal biomarkers (e.g., maternal and cord blood, hair, urine, nails). Each of these exposure approaches has strengths and weaknesses that should be considered in the interpretation of the results, as discussed further in Section 1.6.2.

Fetal and infant mortality

The literature review identified 13 *medium* or *high* confidence epidemiological studies that evaluated the association between iAs exposure and fetal and infant mortality (von Ehrenstein et al., 2006; Shih et al., 2017; Rahman et al., 2007; Rahman et al., 2010; Nyanza et al., 2020; Myers et al., 2010; Milton et al., 2005; Louis et al., 2017; Kwok et al., 2006; Cherry et al., 2008; Cherry et al., 2010; Bloom et al., 2014; Ahmad et al., 2001) (see Figure 3-27). The most commonly assessed outcomes in these studies were spontaneous abortion, stillbirth, neonatal death (death that occurred in the first month of life), infant death (death in the first year of life), and post-neonatal death (death that occurred between 1 month and 12 months of life). Studies that reported these effect estimates are summarized in Figure 3-29 and Figure 3-30.

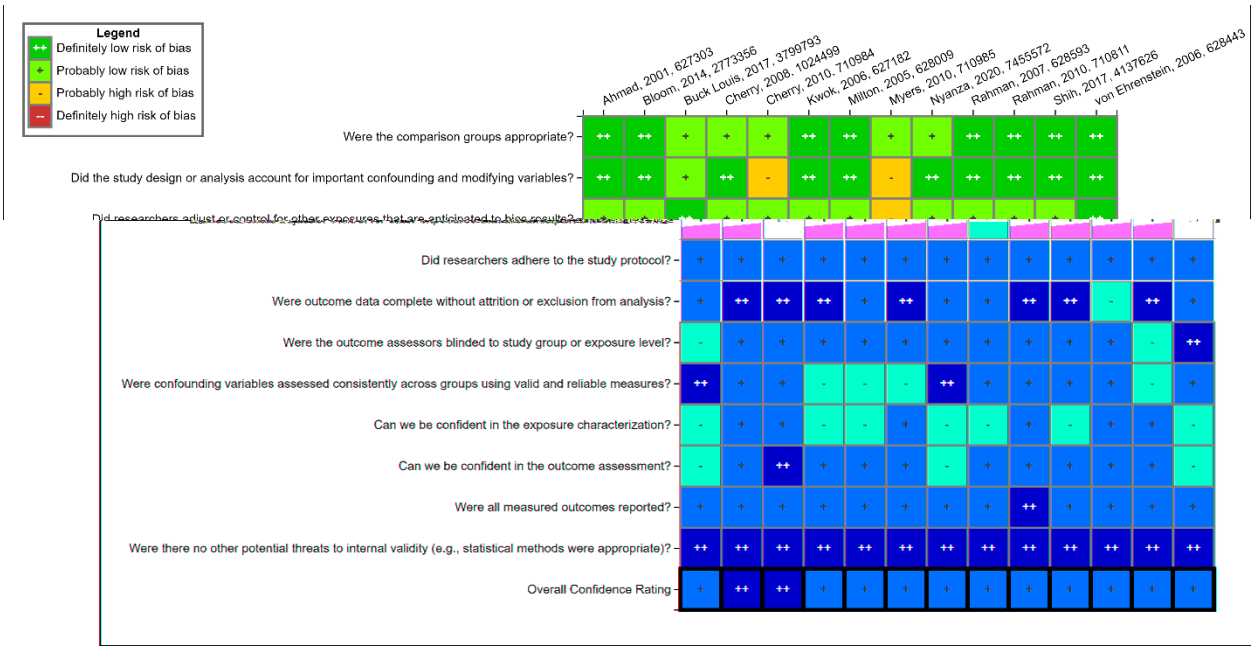


Figure 3-28. Study evaluation ratings for references evaluating fetal and infant mortality (see interactive version in HAWC).

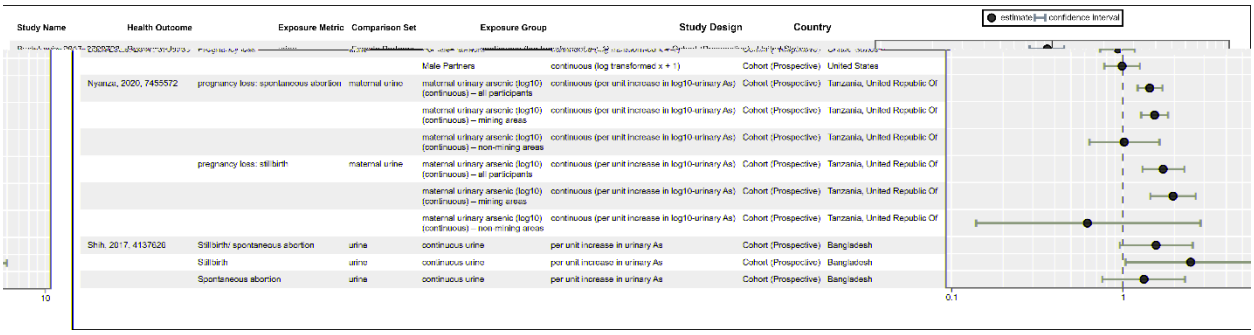
The strongest evidence for an association between iAs exposure and fetal and infant mortality comes from cohort and cross-sectional studies conducted in Bangladesh (Ahmad et al., 2001; Milton et al., 2005; Rahman et al., 2007; Rahman et al., 2010; Shih et al., 2017) and India (von Ehrenstein et al., 2006), where iAs levels in drinking water wells commonly exceed 200 µg/L. Most of these studies reported positive associations between high iAs levels in drinking water (100 µg/L to >2,000 µg/L) and spontaneous abortion, stillbirth, or neonatal mortality. Many of these studies estimated maternal arsenic exposure using iAs levels from the mother's primary drinking water source during pregnancy.

A prospective cohort study in Bangladesh by Rahman et al. (2007) assigned arsenic exposure to 29,134 pregnancies based on iAs levels in well water measured at the time of pregnancy. The authors reported a statistically significant, dose-dependent association between iAs drinking water levels 277–408 µg/L and infant mortality, post-neonatal mortality, and fetal loss (a combination of spontaneous abortion and stillbirth) (see Figure 3-29 and Figure 3-30). They did not observe an association between neonatal mortality at any level of arsenic exposure (Rahman et al., 2007). Another prospective cohort study used the same study population and estimated arsenic exposure using total urinary arsenic concentrations collected from 1,725 pregnant women at gestational week 8 (GW 8) and GW 30 (Rahman et al., 2010). That study found a statistically significant association between total urinary arsenic levels and infant mortality in the highest arsenic exposure group (268–2,019 µg/L) (see Figure 3-30). The authors of this study also identified an association between urinary arsenic levels and increased stillbirths and spontaneous abortions, but these associations did not reach statistical significance. The authors comment that

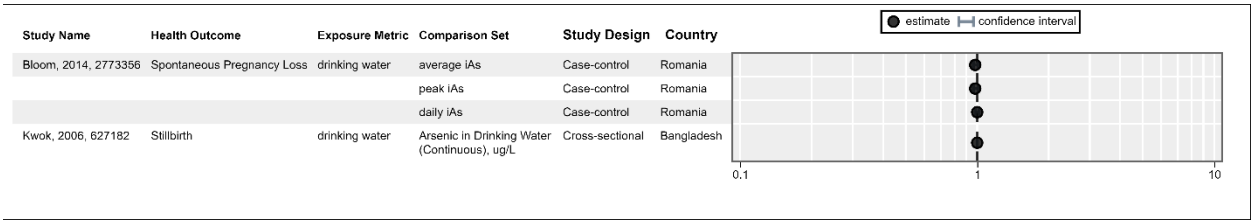
both of these endpoints might be affected by exposure or outcome misclassification, resulting in a dilution of the odds ratio and resulting non-significance (Rahman et al., 2010). Shih et al. (2017) analyzed a cohort of highly exposed women with manifest arsenical skin lesions nested within a larger clinical trial and observed increases in infant mortality and fetal loss (stillbirth or spontaneous abortion) associated with creatinine-adjusted urinary total arsenic concentrations above the median level (i.e., 555 μg/g creatinine) (see Figure 3-29). They also reported smaller positive associations when creatinine-adjusted urinary total arsenic concentrations were evaluated on a continuous scale (i.e., per 50 μg/g creatinine increase). Louis et al. (2017) followed 501 couples from Michigan and Texas intending to become pregnant in a prospective cohort study. Of the 344 couples that confirmed a pregnancy, urinary arsenic concentrations (mean = 9.12–11.45 μg/g) from neither the female nor the male partner were associated with pregnancy loss.

An additional prospective cohort study evaluated associations between prenatal maternal arsenic and birth outcomes in communities with and without artisanal and small-scale gold mining (ASGM) in Tanzania (Nyanza et al., 2020). In communities with ASGM, the authors observed that increased total urinary arsenic obtained via maternal urine sample during the second trimester of pregnancy (median (IQR) = 9.6 (5.1–15.9) μg/L) was associated with a statistically significant increased risk of spontaneous abortion and stillbirth (see Figure 3-29).

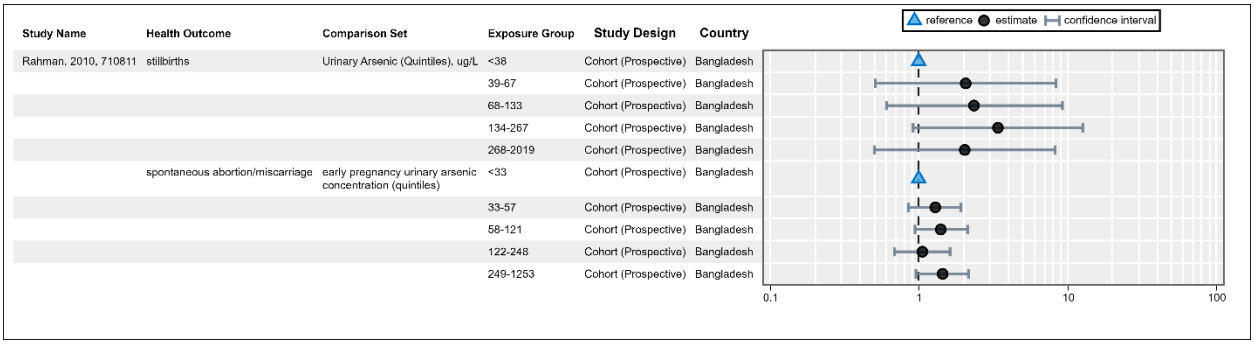
In a cross-sectional study conducted in Bangladesh, Milton et al. (2005) used a single well water measurement from village tube wells to estimate iAs exposure during pregnancy among a group of mothers. The authors reported a strong, statistically significant association between drinking water iAs levels >50 μg/L (measured after pregnancy) and neonatal mortality, spontaneous abortion, and stillbirth (see Figure 3-29). Similarly, von Ehrenstein et al. (2006) conducted a cross-sectional study in India and measured iAs levels in the village tube wells that mothers had used for at least 6 months after their first pregnancies. They reported a statistically significant increase in stillbirths in the highest (≥200 μg/L) iAs exposure category and a nonsignificant, positive association between arsenic and infant mortality. No association was observed between arsenic exposure and spontaneous abortion (see Figure 3-29). In another cross-sectional study, Kwok et al. (2006) observed no association between iAs drinking water levels (exposure categories ranging from 0 to >300 μg/L) and stillbirth in Bangladesh. Fetal death due to arsenic exposure could have been underestimated because the authors noted that these women typically did not receive early prenatal care.



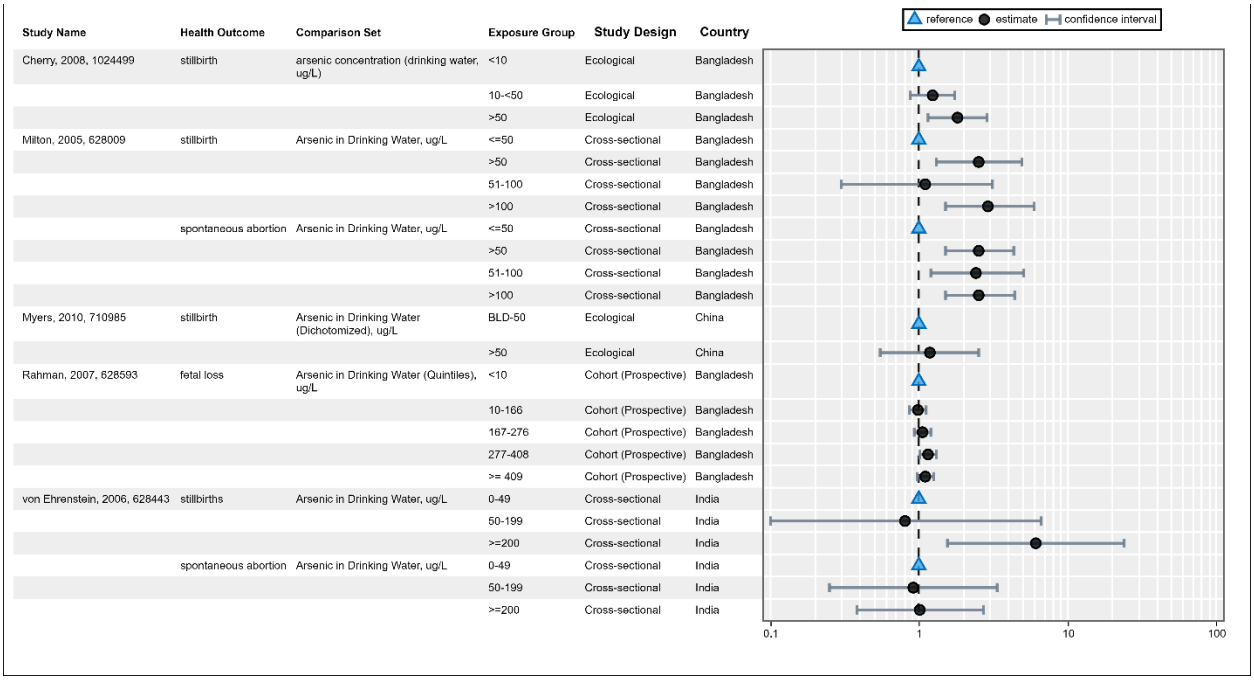
(a) fetal mortality, ratio measures, urine, continuous exposure



(b) fetal mortality, ratio measures, drinking water, continuous exposure



(c) fetal mortality, ratio measures, urine, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Cherry, 2008, 1024499	stillbirth	arsenic concentration (drinking water, ug/L)	<10	Ecological	Bangladesh
			10-<50	Ecological	Bangladesh
			>50	Ecological	Bangladesh
Milton, 2005, 628009	stillbirth	Arsenic in Drinking Water, ug/L	<=50	Cross-sectional	Bangladesh
			>50	Cross-sectional	Bangladesh
			51-100	Cross-sectional	Bangladesh
			>100	Cross-sectional	Bangladesh
	spontaneous abortion	Arsenic in Drinking Water, ug/L	<=50	Cross-sectional	Bangladesh
			>50	Cross-sectional	Bangladesh
			51-100	Cross-sectional	Bangladesh
			>100	Cross-sectional	Bangladesh
Myers, 2010, 710985	stillbirth	Arsenic in Drinking Water (Dichotomized), ug/L	BLD-50	Ecological	China
			>50	Ecological	China
Rahman, 2007, 628593	fetal loss	Arsenic in Drinking Water (Quintiles), ug/L	<10	Cohort (Prospective)	Bangladesh
			10-166	Cohort (Prospective)	Bangladesh
			167-276	Cohort (Prospective)	Bangladesh
			277-408	Cohort (Prospective)	Bangladesh
			>= 409	Cohort (Prospective)	Bangladesh
von Ehrenstein, 2006, 628443	stillbirths	Arsenic in Drinking Water, ug/L	0-49	Cross-sectional	India
			50-199	Cross-sectional	India
			>=200	Cross-sectional	India
	spontaneous abortion	Arsenic in Drinking Water, ug/L	0-49	Cross-sectional	India
			50-199	Cross-sectional	India
			>=200	Cross-sectional	India

(d) fetal mortality, ratio measures, drinking water, categorical exposure

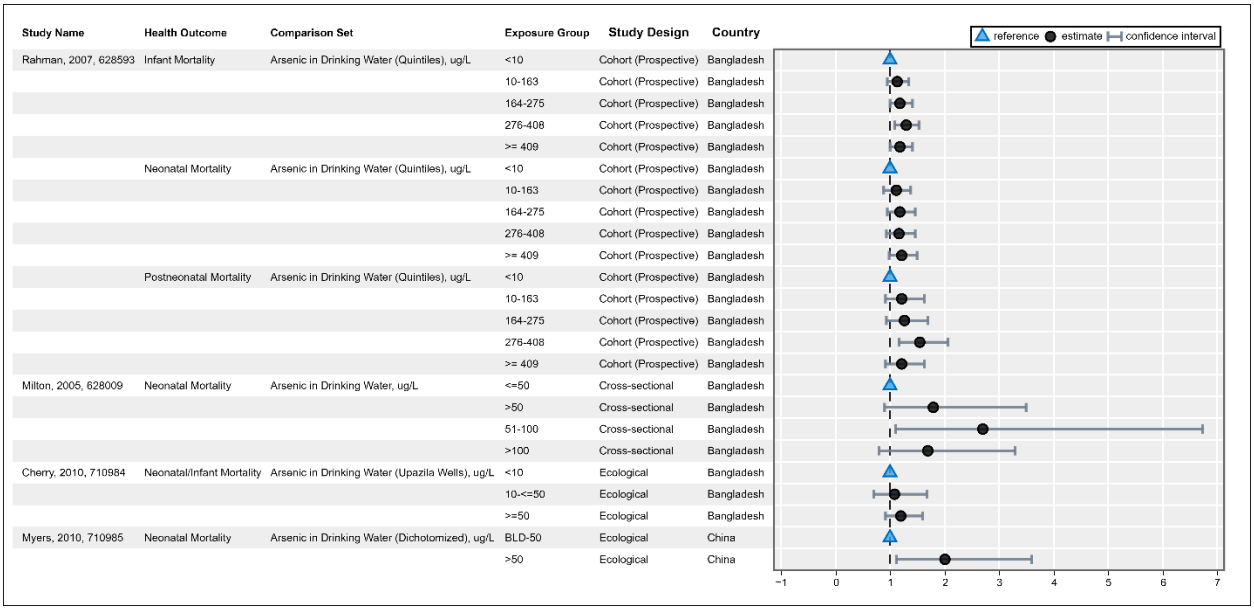
Figure 3-29. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and stillbirth, fetal loss, and spontaneous abortion (a) ratio measures, urine, continuous exposure; (b) ratio measures, drinking water, continuous exposure; (c) ratio measures, urine, categorical exposure; (d) ratio measures, drinking water, categorical exposure.

The systematic literature review also identified one case-control study. This study, conducted in Romania by Bloom et al. (2014), observed no association between arsenic and spontaneous pregnancy loss based on estimated iAs exposure from residential drinking water.

Ecological studies also were identified and reviewed. All ecological studies of *medium* confidence reviewed (with long well-defined exposure periods, limited population migration, large sample sizes, and use of extensive covariates in the analysis) reported a positive association between arsenic exposure in drinking water (up to 860 µg/L) and some measure of infant mortality. Three ecological studies, two conducted in Bangladesh (Cherry et al., 2008; Cherry et al., 2010) and one from China (Myers et al., 2010), used county-level data on iAs levels in drinking water to estimate maternal arsenic exposure (see Figure 3-29 and Figure 3-30). At iAs drinking water levels >50 µg/L, Cherry et al. (2008) and Myers et al. (2010) reported statistically significant associations between stillbirth and neonatal mortality, respectively. Cherry et al. (2010) found a nonsignificant, dose-dependent increase in neonatal/infant mortality within the first year of life.

Summary

Across varying geographic regions (e.g., China, Bangladesh, India, Tanzania), study designs (e.g., cross-sectional, cohort, ecological), and outcome metrics (e.g., spontaneous abortion, stillbirth, infant death, neonatal death, and post-neonatal death) there is general consistency in the association between arsenic exposure and fetal and infant mortality from *medium* and *high* confidence studies. The strongest evidence is from areas with the highest exposure levels (e.g., >200 µg/L arsenic in drinking water), but there also effects observed at lower exposure levels (e.g., <100 µg/L arsenic in drinking water). A dose-response gradient was observed within some [e.g., (Cherry et al., 2008; Cherry et al., 2010)] but not all studies. Some other studies suggested possible dose-response gradients, but these were attenuated at higher exposure levels [e.g., (Rahman et al., 2007; Rahman et al., 2010; Milton et al., 2005)]. There is also some evidence of a dose-response gradient across studies based on stronger effects from higher exposure regions [e.g., (Shih et al., 2017)] compared with lower exposure regions (Louis et al., 2017). There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.



(a) Infant mortality, ratio measures, drinking water, categorical exposure

Figure 3-30. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and infant/neonatal death: ratio measures, drinking water, categorical exposure (see interactive data graphic).

Birth weight

The systematic literature review identified 37 *medium* or *high* confidence epidemiological studies that evaluated the relationship between iAs and birth weight (see Figure 3-31). Most studies demonstrated inverse associations between arsenic exposure and birth weight using a variety of exposure assessment methods and across diverse geographic areas with a range of exposure levels, though not all were statistically significant (see Figure 3-32). It should be noted that gestational age (discussed below in the section, *Prematurity*) may be considered a mediator in the relationship between arsenic and birth weight (see Section 1.6.2). Studies discussed in this hazard section may have considered gestational age as a mediator or a confounder in their analyses. Converging findings using these varying approaches to adjustment provide more confidence in the overall conclusions and indicate a logical coherence in the evidence base.

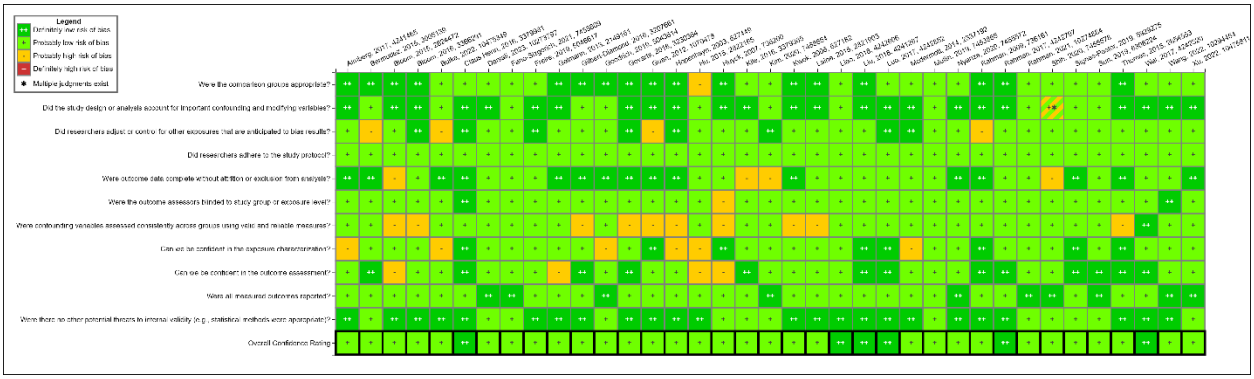


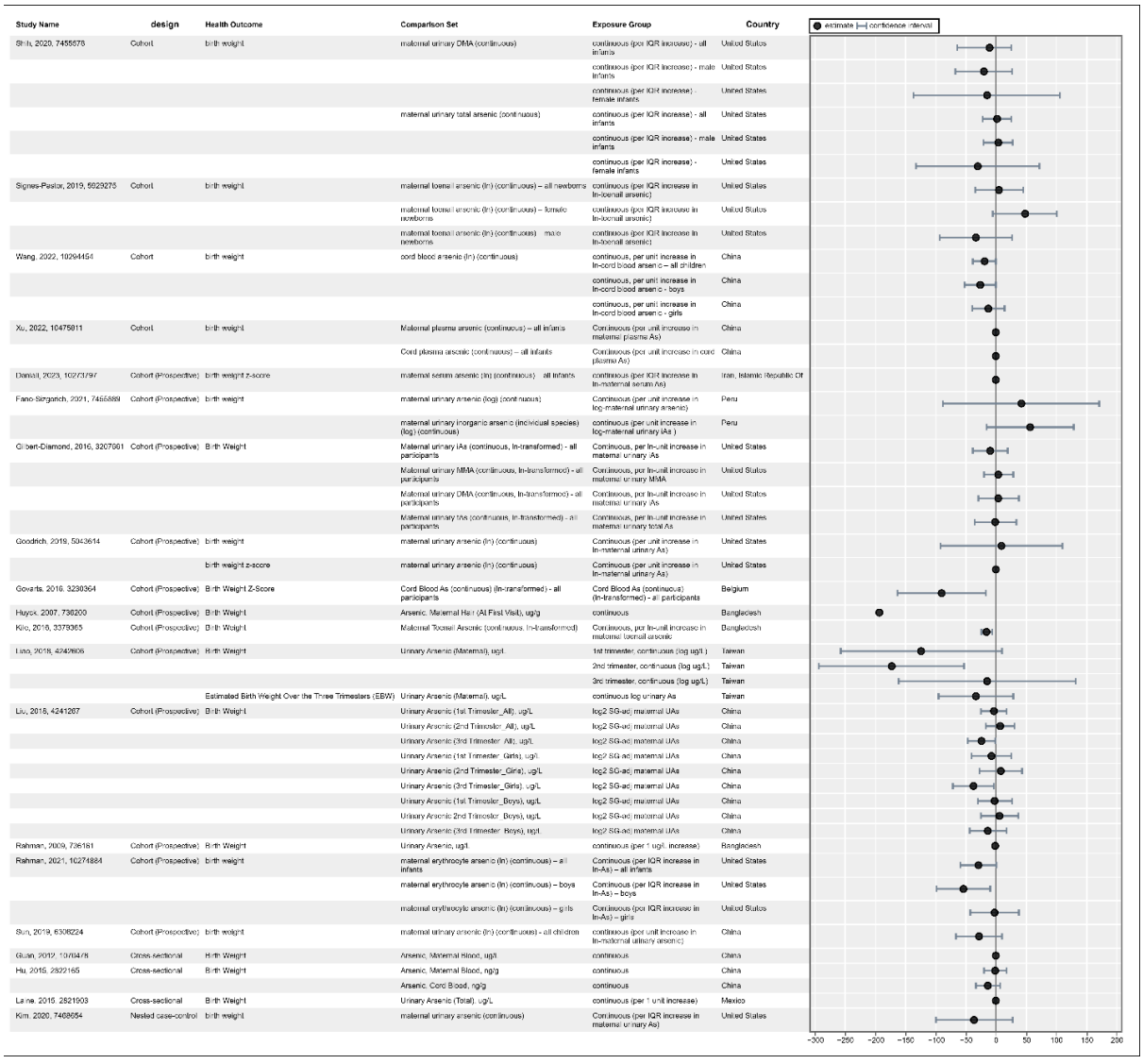
Figure 3-31. Thumbnail schematic of study evaluation ratings for references evaluating birth weight (see interactive version in HAWC).

Twenty-seven cohort and case-control studies conducted across various geographic regions provide the highest-quality evidence of the relationship between iAs exposure and changes in birth weight (Wai et al., 2017; Thomas et al., 2015; Sun et al., 2019; Signes-Pastor et al., 2019a; Shih et al., 2020; Rahman et al., 2009; Rahman et al., 2017b; Rahman et al., 2021; Nyanza et al., 2020; Mullin et al., 2019; Mcdermott et al., 2014; Liu et al., 2018; Liao et al., 2018; Kim et al., 2020; Kile et al., 2016; Huyck et al., 2007; Hopenhayn et al., 2003; Govarts et al., 2016; Goodrich et al., 2019; Gilbert-Diamond et al., 2016; Freire et al., 2019; Fano-Sizgorich et al., 2021; Daniali et al., 2023; Bulka et al., 2022; Bloom et al., 2015; Bloom et al., 2016; Almberg et al., 2017).

Nineteen of these studies observed inverse associations with birth weight, though not all effect estimates were statistically significant and some estimates were only significant in certain strata (Sun et al., 2019; Rahman et al., 2009; Rahman et al., 2017b; Rahman et al., 2021; Nyanza et al., 2020; Mullin et al., 2019; Mcdermott et al., 2014; Liu et al., 2018; Liao et al., 2018; Kim et al., 2020; Kile et al., 2016; Huyck et al., 2007; Hopenhayn et al., 2003; Govarts et al., 2016; Gilbert-Diamond et al., 2016; Freire et al., 2019; Daniali et al., 2023; Bulka et al., 2022; Bloom et al., 2016; Almberg et al., 2017); (see Figure 3-32). For example, Rahman et al. (2009) measured total urinary

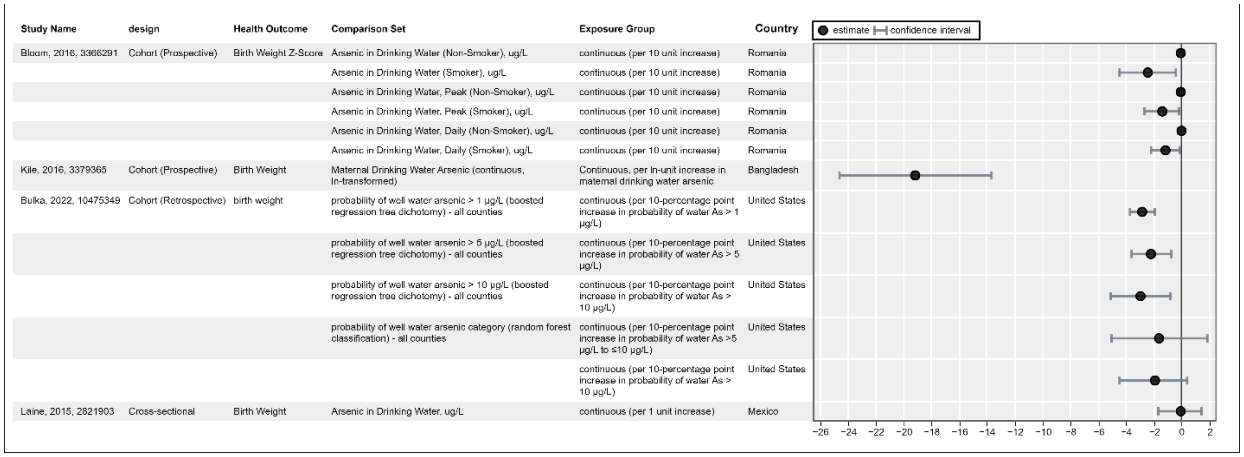
arsenic in pregnant mothers from a highly exposed population in Bangladesh at approximately GW 8 and GW 30. The authors observed a statistically significant, inverse association between average maternal urinary arsenic levels (mean (SD) of GW 8 and GW 30 urinary arsenic: 160 (163) μg/L) and birth weight (beta (SE): −1.68 (0.62)). In addition, a small prospective cohort study of 49 subjects in Bangladesh found a statistically significant inverse association between maternal arsenic levels in hair (0.14–3.28 μg/g) at their first prenatal visit (before GW 28) and birth weight (beta (SE): −193.5 (90)) (Huyck et al., 2007). Rahman et al. (2017b) observed inverse associations between concentrations of arsenic in drinking water (median = 2.2 μg/L) and birth weight in a prospective cohort study conducted in Bangladesh, with associations mediated through gestational age as well as based on pathways independent of gestational age. The decreases in birth weight associated with arsenic exposure were greater in magnitude for babies with lower birth weight. For example, for babies with birthweight <2300 g, each unit increase in ln-transformed water arsenic was associated with a 47.7 g decrease (95% CI: −63.1, −29.4) in birthweight, while the results were attenuated for babies with birthweight <2,800 g (−18.7 (−31.3, −5.5)). Results were similar when arsenic measured in toenail samples were used to assign exposure (Rahman et al., 2017b). Kile et al. (2016) measured arsenic in drinking water at the time of enrollment (gestational age <16 weeks) (median: 2.3 μg/L) and in toenails collected ≤1 month postpartum (median: 1.46 μg/g). They observed decreased birth weight for every unit increase in natural log drinking water arsenic (beta (95% CI): −19.17 g (−24.64, −13.69)) and toenail arsenic (beta (95% CI): −15.72 g (−24.52, −6.91)), with associations mediated through gestational age and maternal weight gain during pregnancy.

In Taiwan, Liao et al. (2018) measured arsenic in maternal urine samples from 130 women during each trimester of pregnancy (mean urinary arsenic in each trimester: 40.0–41.8 μg/L) and reported a decrease in estimated birth weight associated with increased arsenic exposure, with strongest and statistically significant effects in the second trimester (beta (95% CI): first trimester: −123.88 g (−258.16, 10.41); second trimester (−173.26 g (−293.56, −52.95); third trimester (−14.51 g (−161.22, 132.20)). Using a similar study design, Liu et al. (2018) measured arsenic in maternal urine samples from 1,390 women in Wuhan, China during each trimester of pregnancy (median SG-adjusted urinary arsenic in each trimester: 20.27–21.86 μg/L). They observed decreases in birth weight associated with third trimester maternal urinary arsenic concentrations (beta (95% CI): −24.27 g (−46.99, −1.55)) but mixed results in earlier trimesters (beta (95% CI): first trimester: −3.89 g (−25.21, 17.42); second trimester (6.79 g (−16.56, 30.13)). In stratified analyses, the significant association in the third trimester persisted for girls (beta (95% CI): −37.66 g (−71.57, −3.75)) but was attenuated for boys (beta (95% CI): −13.57 g (−44.26, 17.13)).



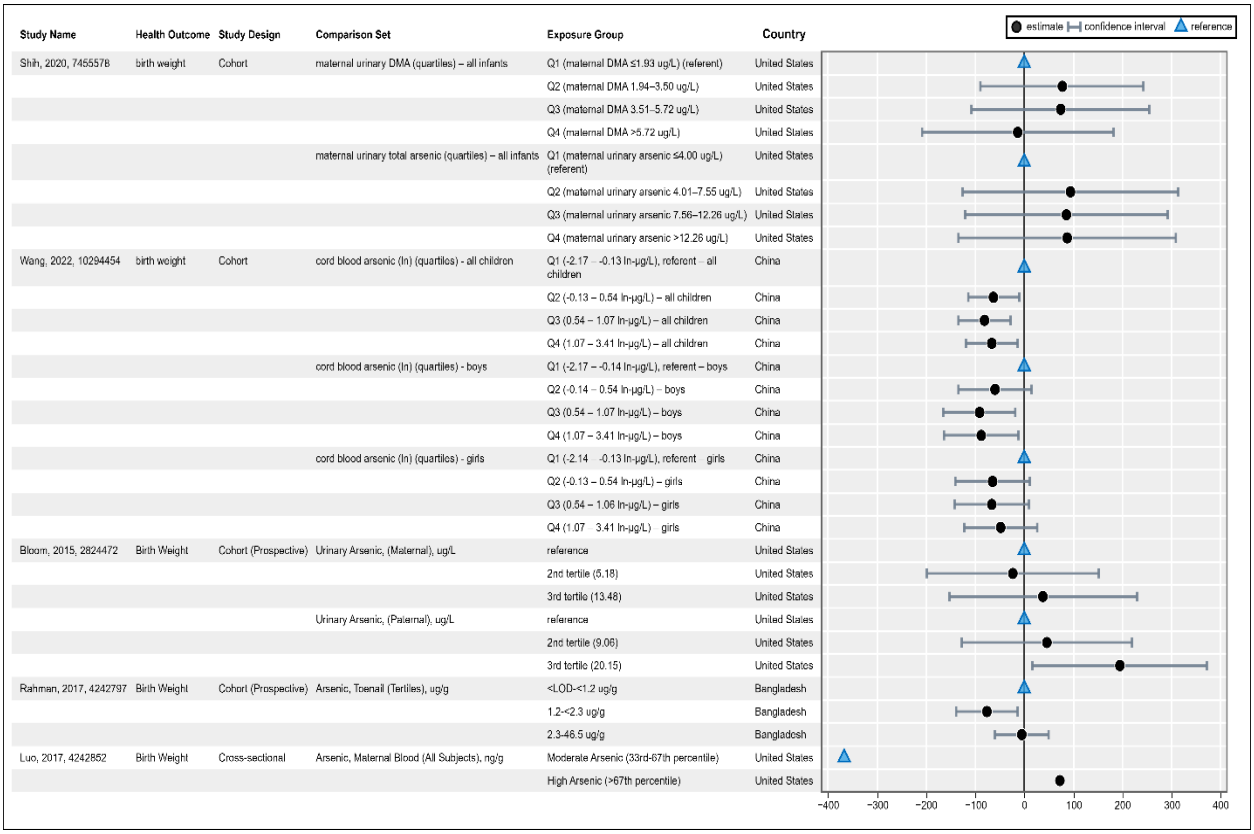
Study Name	design	Health Outcome	Comparison Set	Exposure Group	Country
Shih, 2020, 7455578	Cohort	birth weight	maternal urinary DMA (continuous)	continuous (per IQR increase) - all infants	United States
				continuous (per IQR increase) - male infants	United States
				continuous (per IQR increase) - female infants	United States
			maternal urinary total arsenic (continuous)	continuous (per IQR increase) - all infants	United States
				continuous (per IQR increase) - male infants	United States
				continuous (per IQR increase) - female infants	United States
Signes-Pastor, 2019, 5023275	Cohort	birth weight	maternal toenail arsenic (ln) (continuous) – all newborns	continuous (per IQR increase in ln-toenail arsenic)	United States
			maternal toenail arsenic (ln) (continuous) – female newborns	continuous (per IQR increase in ln-toenail arsenic)	United States
			maternal toenail arsenic (ln) (continuous) – male newborns	continuous (per IQR increase in ln-toenail arsenic)	United States
Wang, 2022, 10294454	Cohort	birth weight	cord blood arsenic (ln) (continuous)	continuous, per unit increase in ln-cord blood arsenic – all children	China
				continuous, per unit increase in ln-cord blood arsenic - boys	China
				continuous, per unit increase in ln-cord blood arsenic - girls	China
Xu, 2022, 10475011	Cohort	birth weight	Maternal plasma arsenic (continuous) – all infants	Continuous (per unit increase in maternal plasma As)	China
			Cord plasma arsenic (continuous) – all infants	Continuous (per unit increase in cord plasma As)	China
Danaei, 2023, 10273797	Cohort (Prospective)	birth weight z-score	maternal serum arsenic (ln) (continuous) - all infants	continuous (per IQR increase in ln-maternal serum As)	Iran, Islamic Republic Of
Fano-Sizgorich, 2021, 7465889	Cohort (Prospective)	birth weight	maternal urinary arsenic (log) (continuous)	Continuous (per unit increase in log-maternal urinary arsenic)	Peru
			maternal urinary inorganic arsenic (individual species) (log) (continuous)	continuous (per unit increase in log-maternal urinary iAs)	Peru
Gilbert-Diamond, 2016, 3207001	Cohort (Prospective)	Birth Weight	Maternal urinary iAs (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary As	United States
			Maternal urinary MMA (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary MMA	United States
			Maternal urinary DMA (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary As	United States
			Maternal urinary tAs (continuous, ln-transformed) - all participants	Continuous, per ln-unit increase in maternal urinary total As	United States
Goodrich, 2019, 5943614	Cohort (Prospective)	birth weight	maternal urinary arsenic (ln) (continuous)	Continuous (per unit increase in ln-maternal urinary As)	United States
		birth weight z-score	maternal urinary arsenic (ln) (continuous)	Continuous (per unit increase in ln-maternal urinary As)	United States
Govarts, 2016, 3230364	Cohort (Prospective)	Birth Weight Z-Score	Cord Blood As (continuous) (ln-transformed) - all participants	Cord Blood As (continuous) (ln-transformed) - all participants	Belgium
Huyck, 2007, 736200	Cohort (Prospective)	Birth Weight	Arsenic, Maternal Hair (At First Visit), ug/g	continuous	Bangladesh
Kile, 2016, 3379365	Cohort (Prospective)	Birth Weight	Maternal Toenail Arsenic (continuous, ln-transformed)	Continuous, per ln-unit increase in maternal toenail arsenic	Bangladesh
Liao, 2019, 4240806	Cohort (Prospective)	Birth Weight	Urinary Arsenic (Maternal), ug/l	1st trimester, continuous (log ug/L)	Taiwan
				2nd trimester, continuous (log ug/L)	Taiwan
				3rd trimester, continuous (log ug/L)	Taiwan
		Estimated Birth Weight Over the Three Trimesters (EBW)	Urinary Arsenic (Maternal), ug/L	continuous log urinary As	Taiwan
Liu, 2018, 4241267	Cohort (Prospective)	Birth Weight	Urinary Arsenic (1st Trimester_All), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (2nd Trimester_All), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (3rd Trimester_All), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (1st Trimester_Girls), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (2nd Trimester_Girls), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (3rd Trimester_Girls), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (1st Trimester_Boys), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic 2nd Trimester_Boys), ug/L	log2 SG-ad maternal UAs	China
			Urinary Arsenic (3rd Trimester_Boys), ug/L	log2 SG-ad maternal UAs	China
Rahman, 2009, 736161	Cohort (Prospective)	Birth Weight	Urinary Arsenic, ug/l	continuous (per 1 ug/L increase)	Bangladesh
Rahman, 2021, 10274884	Cohort (Prospective)	birth weight	maternal erythrocyte arsenic (ln) (continuous) – all infants	Continuous (per IQR increase in ln-As) – all infants	United States
			maternal erythrocyte arsenic (ln) (continuous) – boys	Continuous (per IQR increase in ln-As) – boys	United States
			maternal erythrocyte arsenic (ln) (continuous) – girls	Continuous (per IQR increase in ln-As) – girls	United States
Sun, 2019, 6308224	Cohort (Prospective)	birth weight	maternal urinary arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-maternal urinary arsenic)	China
Guan, 2012, 10764478	Cross-sectional	Birth Weight	Arsenic, Maternal Blood, ug/l	continuous	China
Hu, 2015, 2822165	Cross-sectional	Birth Weight	Arsenic, Maternal Blood, ng/g	continuous	China
			Arsenic, Cord Blood, ng/g	continuous	China
Laine, 2015, 2821903	Cross-sectional	Birth Weight	Urinary Arsenic (Total), ug/L	continuous (per 1 unit increase)	Mexico
Kim, 2020, 7468654	Nested case-control	birth weight	maternal urinary arsenic (continuous)	Continuous (per IQR increase in maternal urinary As)	United States

(a) Birth weight, difference measures, biomarkers, continuous exposure



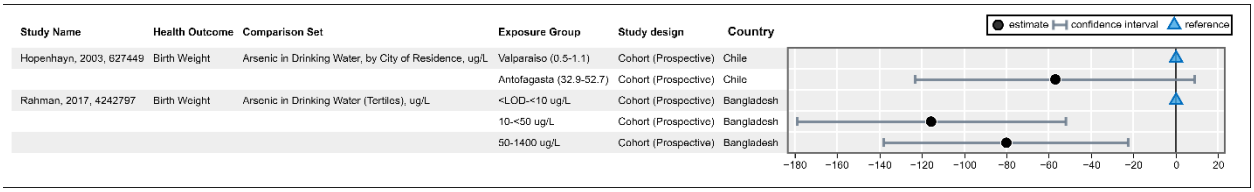
Study Name	design	Health Outcome	Comparison Set	Exposure Group	Country
Bloom, 2016, 3368291	Cohort (Prospective)	Birth Weight Z-Score	Arsenic in Drinking Water (Non-Smoker), ug/L	continuous (per 10 unit increase)	Romania
			Arsenic in Drinking Water (Smoker), ug/L	continuous (per 10 unit increase)	Romania
			Arsenic in Drinking Water, Peak (Non-Smoker), ug/L	continuous (per 10 unit increase)	Romania
			Arsenic in Drinking Water, Peak (Smoker), ug/L	continuous (per 10 unit increase)	Romania
			Arsenic in Drinking Water, Daily (Non-Smoker), ug/L	continuous (per 10 unit increase)	Romania
			Arsenic in Drinking Water, Daily (Smoker), ug/L	continuous (per 10 unit increase)	Romania
Kile, 2016, 3379365	Cohort (Prospective)	Birth Weight	Maternal Drinking Water Arsenic (continuous, ln-transformed)	Continuous, per ln-unit increase in maternal drinking water arsenic	Bangladesh
Bulka, 2022, 10475349	Cohort (Retrospective)	birth weight	probability of well water arsenic > 1 µg/L (boosted regression tree dichotomy) - all counties	continuous (per 10-percentage point increase in probability of water As > 1 µg/L)	United States
			probability of well water arsenic > 5 µg/L (boosted regression tree dichotomy) - all counties	continuous (per 10-percentage point increase in probability of water As > 5 µg/L)	United States
			probability of well water arsenic > 10 µg/L (boosted regression tree dichotomy) - all counties	continuous (per 10-percentage point increase in probability of water As > 10 µg/L)	United States
			probability of well water arsenic category (random forest classification) - all counties	continuous (per 10-percentage point increase in probability of water As >5 µg/L to ≤10 µg/L)	United States
				continuous (per 10-percentage point increase in probability of water As > 10 µg/L)	United States
Laine, 2015, 2821903	Cross-sectional	Birth Weight	Arsenic in Drinking Water, ug/L	continuous (per 1 unit increase)	Mexico

(b) Birth weight, difference measures, drinking water, continuous exposure



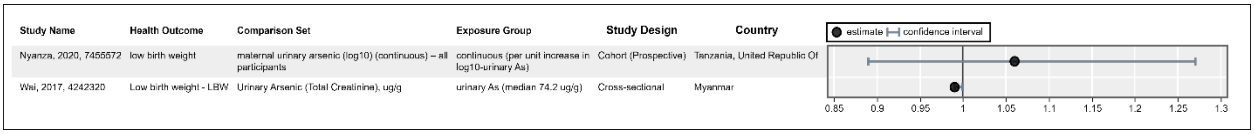
Study Name	Health Outcome	Study Design	Comparison Set	Exposure Group	Country
Shih, 2020, 7455578	birth weight	Cohort	maternal urinary DMA (quartiles) – all infants	Q1 (maternal DMA ≤1.93 ug/L) (referent)	United States
				Q2 (maternal DMA 1.94–3.50 ug/L)	United States
				Q3 (maternal DMA 3.51–5.72 ug/L)	United States
				Q4 (maternal DMA >5.72 ug/L)	United States
			maternal urinary total arsenic (quartiles) – all infants	Q1 (maternal urinary arsenic ≤4.00 ug/L) (referent)	United States
				Q2 (maternal urinary arsenic 4.01–7.55 ug/L)	United States
				Q3 (maternal urinary arsenic 7.56–12.26 ug/L)	United States
				Q4 (maternal urinary arsenic >12.26 ug/L)	United States
Wang, 2022, 10294454	birth weight	Cohort	cord blood arsenic (ln) (quartiles) - all children	Q1 (-2.17 – -0.13 ln-µg/L), referent - all children	China
				Q2 (-0.13 – 0.54 ln-µg/L) – all children	China
				Q3 (0.54 – 1.07 ln-µg/L) – all children	China
				Q4 (1.07 – 3.41 ln-µg/L) – all children	China
			cord blood arsenic (ln) (quartiles) - boys	Q1 (-2.17 – -0.14 ln-µg/L), referent – boys	China
				Q2 (-0.14 – 0.54 ln-µg/L) - boys	China
				Q3 (0.54 – 1.07 ln-µg/L) – boys	China
				Q4 (1.07 – 3.41 ln-µg/L) – boys	China
			cord blood arsenic (ln) (quartiles) - girls	Q1 (-2.14 -0.13 ln-µg/L), referent girls	China
				Q2 (-0.13 – 0.54 ln-µg/L) – girls	China
				Q3 (0.54 – 1.06 ln-µg/L) – girls	China
				Q4 (1.07 3.41 ln-µg/L) girls	China
Bloom, 2015, 2824472	Birth Weight	Cohort (Prospective)	Urinary Arsenic, (Maternal), ug/L	reference	United States
				2nd tertile (5.18)	United States
				3rd tertile (13.48)	United States
			Urinary Arsenic, (Paternal), ug/L	reference	United States
				2nd tertile (9.06)	United States
				3rd tertile (20.15)	United States
Rahman, 2017, 4242797	Birth Weight	Cohort (Prospective)	Arsenic, Toenail (Tertiles), ug/g	<LOD-<1.2 ug/g	Bangladesh
				1.2-<2.3 ug/g	Bangladesh
				2.3-46.5 ug/g	Bangladesh
Luo, 2017, 4242852	Birth Weight	Cross-sectional	Arsenic, Maternal Blood (All Subjects), ng/g	Moderate Arsenic (33rd-67th percentile)	United States
				High Arsenic (>67th percentile)	United States

(c) Birth weight, difference measures, biomarkers, categorical exposure



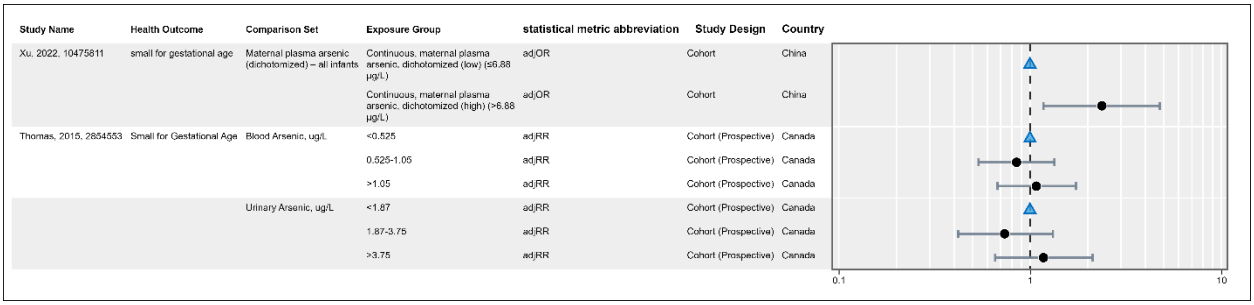
Study Name	Health Outcome	Comparison Set	Exposure Group	Study design	Country
Hopenhayn, 2003, 627449	Birth Weight	Arsenic in Drinking Water, by City of Residence, ug/L	Valparaiso (0.5-1.1)	Cohort (Prospective)	Chile
			Antofagasta (32.9-52.7)	Cohort (Prospective)	Chile
Rahman, 2017, 4242797	Birth Weight	Arsenic in Drinking Water (Tertiles), ug/L	<LOD-<10 ug/L	Cohort (Prospective)	Bangladesh
			10-<50 ug/L	Cohort (Prospective)	Bangladesh
			50-1400 ug/L	Cohort (Prospective)	Bangladesh

(d) Birth weight, difference measures, drinking water, categorical exposure



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Nyanza, 2020, 7455572	low birth weight	maternal urinary arsenic (log10) (continuous) – all participants	continuous (per unit increase in log10-urinary As)	Cohort (Prospective)	Tanzania, United Republic Of
Wai, 2017, 4242320	Low birth weight - LBW	Urinary Arsenic (Total Creatinine), ug/g	urinary As (median 74.2 ug/g)	Cross-sectional	Myanmar

(e) Low birth weight – ratio measures – biomarkers – continuous exposure



(f) Small for gestational age – ratio measures – biomarkers -categorical exposure

Figure 3-32. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and birth weight (a) birth weight, difference measures, biomarkers, continuous exposures; (b) birth weight, difference measures, drinking water, continuous exposures; (c) birth weight, difference measures, biomarkers, categorical exposures; (d) birth weight, difference measures, drinking water, categorical exposures; (e) low birth weight, ratio measures, biomarkers, continuous exposures; (f) Small for gestational age, ratio measures, biomarkers, categorical exposures (see interactive data graphic).

Hopenhayn et al. (2003) conducted a prospective cohort study in two Chilean towns, Antofagasta, and Valparaiso, with high (30–40 µg/L) or low (<1 µg/L) iAs levels in the drinking water, respectively. Babies born to women living in Antofagasta (high arsenic exposure) had lower average birth weight compared with babies born to women living in Valparaiso (low arsenic exposure) (beta (95% CI): −57 g (−123, 9)). Results were similar but attenuated when using an individual-level measure of exposure (beta (95% CI) per µg arsenic: −0.26 g (−0.85, 0.31)). The authors also found that the association between iAs and birth weight was nearly twice as large in preterm infants (beta (95% CI): −107 g (−265, 50)) compared with full-term infants (beta (95% CI): −44 g (−115, 27)), but the interaction was not statistically significant (Hopenhayn et al., 2003). Bloom et al. (2016) conducted a preliminary cohort study using pregnant women (n = 122) to evaluate low-level arsenic exposure (<10 µg/L) and birth outcomes. Study authors found that exposure to higher average arsenic concentrations (10 µg/L) was associated with lower birth weight z-score among smokers (beta (95% CI): −2.45 (−4.49, −0.42)).

Six cohort studies observed associations with increased birth weight, though most of these effect estimates were not statistically significant (Signes-Pastor et al., 2019a; Shih et al., 2020; Mullin et al., 2019; Goodrich et al., 2019; Fano-Sizgorich et al., 2021; Bloom et al., 2015). For example, in a small (n = 56) cohort based in Michigan with geometric mean maternal urinary arsenic of 4.3 µg/L, Goodrich et al. observed a suggestive positive association with birthweight (beta (95% CI): 9.03 g (−92.34, 110.39)) (Goodrich et al., 2019). Bloom et al. (2015) conducted a prospective cohort study using the LIFE cohort in the United States. They found no association between preconception maternal (mean: 17.13 µg/L) or paternal (mean: 19.65 µg/L) total urinary arsenic levels and birth weight, except for a statistically significant, positive association between

the highest tertile of paternal urinary arsenic levels (≥20.15 μg/L) and birth weight (beta (95% CI): 194.71 g (17.13, 372.30)).

Ten cross-sectional studies that evaluated the association between arsenic and birth weight also were identified in the literature search (Xu et al., 2022; Wang et al., 2022a; Luo et al., 2017; Laine et al., 2015; Kwok et al., 2006; Hu et al., 2015; Guan et al., 2012; Gelmann et al., 2013; Claus Henn et al., 2016; Bermudez et al., 2015) (see Figure 3-32). Luo et al. (2017) measured As in whole blood samples (median ~ 0.044 μg/dL) collected in the first trimester of pregnancy from 275 women in North Carolina. Moderate arsenic exposure (i.e., maternal whole blood arsenic concentrations between the 33rd and 67th percentiles), but not high arsenic exposure (i.e., >67th percentile) were associated with decreases in birthweight (beta (SE): −366.5 g (175.2)). The decrease in birthweight associated with moderate arsenic exposure was greater in male infants (beta (SE): −870.69 g (372.09)) and nonsmoking mothers (beta (SE): −464.29 g (202.74)). Guan et al. (2012) studied an urban population in China and measured arsenic levels in cord blood and maternal blood at delivery. They reported median arsenic concentrations of 5.30 and 3.71 μg/L in maternal and cord blood, respectively. Guan et al. (2012) observed a statistically significant, inverse association between maternal blood arsenic levels and birth weight beta (*p*-value): −0.19 kg (0.015)). Two other cross-sectional studies in China evaluating exposure via maternal blood arsenic (median = 5.45 μg/L) and cord blood arsenic (median = 1.71–5.38 μg/L) also reported inverse associations between blood arsenic concentrations and birth weight (cord blood beta (95% CI): −19.39 g (−38.14, −0.63); cord blood beta (95% CI): −0.028 kg (−0.041, −0.016); maternal blood beta (95% CI): −0.027 kg (−0.041, −0.013)) (Xu et al., 2022; Wang et al., 2022a).

However, some cross-sectional studies reported null results or estimates whose confidence intervals included the null. For example, one study conducted in Bangladesh found no association between drinking water iAs levels (median across regions: 24–139 ppb) and odds of low birth weight (OR (95% CI): 0.99 (0.99, 1.00) (Kwok et al., 2006). Similarly, a cross-sectional study conducted in China by Hu et al. (2015) observed a non-statistically significant inverse association between both maternal and cord blood arsenic levels (median = 11.0 and 10.4 ng/g, respectively) and birth weight (maternal blood beta (95% CI): −1.5 g (−20.2, 17.3)); cord blood beta (95% CI): −13.6 (−33.9, 6.7)). Laine et al. (2015) conducted a cross-sectional study in Mexico and estimated arsenic exposure using drinking water iAs levels shortly after birth (mean = 24.6 μg/L) and maternal urinary arsenic levels before birth (mean iAs = 2.1μg/L). They observed a non-statistically significant association with reduced birth weight (drinking water beta (95% CI): −0.1 g (−1.7, 1.4); maternal urine beta (95% CI): −21.7 g (−46.8, 3.4)). In a study conducted in Romania, Gelmann et al. (2013) estimated iAs exposure using both maternal urinary and drinking water iAs levels. Drinking water iAs levels were not significantly different between women who had low-birth-weight babies (56.9 ± 24.7 μg/L) or normal-birth-weight babies (52.2 ± 30.0 μg/L). For these and other "non-significant" findings, it should be noted that even changes that are not statistically significant could be biologically significant and also that changes that are not significant at the individual level could

be meaningful at the population level (Gilbert and Weiss, 2006). Among women classified as "exposed" (iAs concentrations in drinking water ≥10 µg/L), however, women who delivered low-birth-weight babies had a significantly higher prevalence of maternal urinary iAs levels >9 µg/L (67%) compared with women with normal-birth-weight outcomes (10%). The authors also found that none of the exposed women with normal-birth-weight infants had a urine iAs concentration ≥10 µg/L and suggested that this might be due to maternal differences in arsenic metabolism (methylation) and excretion (Gelmann et al., 2013).

Summary

High and *medium* confidence studies across diverse geographic regions (e.g., China, United States, Chile, Bangladesh) representing a range of exposure levels and utilizing a variety of exposure assessment methods provide generally consistent results indicating statistically significant and nonsignificant inverse associations between iAs and birth weight. This association may be mediated by gestational age (see Section on *Prematurity*, below). There is some evidence for a dose-response gradient, though the gradient was attenuated at higher levels [e.g., (Wang et al., 2022a)]. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.

Fetal growth

Eighteen *medium* or *high* confidence epidemiological studies were identified that measured indices of fetal growth in utero or at birth (see Figure 3-33). Approximately half of these studies used total urinary maternal arsenic levels to estimate exposure (Sun et al., 2019; Shih et al., 2020; Louis et al., 2017; Liu et al., 2018; Liao et al., 2018; Kippler et al., 2012; Kim et al., 2020; Goodrich et al., 2019; Fano-Sizgorich et al., 2021; Davis et al., 2015).

There were 12 cohort or case-control studies evaluating the association between arsenic and fetal growth measures (Sun et al., 2019; Signes-Pastor et al., 2019a; Shih et al., 2020; Röllin et al., 2016; Rahman et al., 2021; Liu et al., 2018; Liao et al., 2018; Kim et al., 2020; Goodrich et al., 2019; Freire et al., 2019; Fano-Sizgorich et al., 2021; Daniali et al., 2023). Cohort studies conducted in Taiwan (Liao et al., 2018)and Wuhan, China (Liu et al., 2018) observed statistically significant associations between maternal urinary arsenic and impaired fetal growth (see Figure 3-33). Liao et al. (2018) measured arsenic in maternal urine samples from 130 women during each trimester of pregnancy (geometric mean by trimester: first trimester = 41.8 µg/L; second trimester = 40.0 µg/L; third trimester = 40.6 µg/L) and reported a statistically significant decrease in head circumference birth in association with increased second trimester maternal arsenic exposure (beta (95% CI): −0.61 cm (−1.07, −0.15)). They also observed a significant decrease in chest circumference in association with increased first and second trimester maternal urinary arsenic (first trimester beta (95% CI): −0.72 cm (−1.32, −0.12); second trimester beta (95% CI): −0.65 cm (−1.20, −0.11)) as well a significant decrease in biparietal diameter in relation to urinary arsenic over all three trimesters (beta (95% CI): −1.05 mm (−1.95, −0.15)). Liu et al. (2018) measured arsenic in

maternal urine samples from 1,390 women during each trimester of pregnancy. They observed decreases in birth length associated with arsenic concentrations measured in maternal urine during the third trimester of pregnancy (median = 13.59 μg/L; beta (95% CI): −0.13 cm (−0.22, −0.04)). In stratified analyses, these associations persisted for girls (beta (95% CI): −0.18 cm (−0.31, −0.05)), but were attenuated for boys (beta (95% CI): −0.09 (−0.21, 0.03)) (see Figure 3-33). However, another study in China observed suggestive but null effects of second trimester maternal urinary arsenic (geometric mean = 20.03 μg/L) on birth length (beta (95% CI): −0.13 cm (−0.28, 0.03)) (Sun et al., 2019).

There were also nine cohort or case-control studies based in North America, with mixed findings. Two studies observed statistically significant inverse associations between maternal arsenic (geometric mean urinary arsenic = 4.3 μg/L; median toenail arsenic = 0.05 μg/g) and fetal growth parameters: femur length [beta (95% CI): −0.26 mm (−0.46, −0.07)] (Goodrich et al., 2019); head circumference (males only) [beta (95% CI): −0.20 cm (−0.38, −0.02)] (Signes-Pastor et al., 2019a). Three studies observed statistically significant positive associations between maternal urinary arsenic during pregnancy (median = 3.96–7.7 μg/L) and fetal growth parameters: birth length [beta (95% CI): 0.28 cm (0.14, 0.42) (Shih et al., 2020); 0.22 cm (0.01, 0.44) (Signes-Pastor et al., 2019a)]; head circumference [beta (95% CI): 0.12 (0.04, 0.21)(Shih et al., 2020)]. Two studies documented no association with fetal growth parameters (Rahman et al., 2021; Kim et al., 2020).

Studies in other parts of the world (Spain, Peru, and Iran) did not observe any statistically significant associations with fetal growth parameters when assessing arsenic via urine (geometric mean total urinary arsenic = 43.97 μg/L), placenta (median <0.004 ng/g), or blood (geometric mean = 2.21 μg/L) (Freire et al., 2019; Fano-Sizgorich et al., 2021; Daniali et al., 2023).

Six cross-sectional studies were also identified (Xu et al., 2022; Wang et al., 2022a; Lee et al., 2021; Kippler et al., 2012; Davis et al., 2015; Claus Henn et al., 2016). Four of these studies evaluated fetal growth endpoints at birth in relation to maternal or cord blood (Xu et al., 2022; Wang et al., 2022a; Lee et al., 2021; Claus Henn et al., 2016). Mixed findings were observed (see Figure 3-34). One study in China did not observe associations between cord blood arsenic (median (IQR) = 1.71 (2.03) μg/L) and birth length (beta (95% CI): 0.01 cm (−0.01, 0.21)) or head circumference (beta (95% CI): 0.01 cm (−0.03, 0.06)) (Wang et al., 2022a), while another study in China observed inverse associations for both birth length and head circumference in relation to maternal blood arsenic (median (range) = 5.45 (0.7–17.1) μg/L; beta (95% CI): birth length: −0.12 cm (−0.18, −0.06); head circumference: −0.05 cm (−0.09, −0.01)). Results were similar for cord blood arsenic (median (range) = 5.38 (0.7–23.6) μg/L) (Xu et al., 2022). In a population in the U.S. living near a mining-related Superfund site, maternal blood arsenic (median (IQR) = 1.4 (0.97–2.3) μg/L) – but not cord blood arsenic (median (IQR) = 2.4 (1.8–3.3) μg/L) – was associated with decreased head circumference (beta (95% CI): −0.22 cm (−0.42, −0.03)) (Claus Henn et al., 2016). The remaining two cross-sectional studies evaluated exposure via maternal urinary samples and evaluated fetal growth during gestation (Kippler et al., 2012; Davis et al., 2015). In a study based in

Bangladesh, Kippler et al. (2012) measured total urinary arsenic concentrations in mothers at GW 8 (median = 79 μg/L) and GW 30 (median = 85 μg/L) and evaluated five endpoints of fetal size by ultrasound at GW 14 and GW 30, including three fetal head measurements (head circumference, biparietal diameter, occipitofrontal diameter), abdominal circumference, and femur length. At GW 14, the authors observed a statistically significant, inverse association between maternal urinary arsenic levels at GW 8 and occipitofrontal diameter z-score (beta (95% CI): −0.06 (−0.11, −0.008)). At GW 30, a statistically significant association was found between decreased femur length z-score and maternal urinary arsenic levels at GW 30 (beta (95% CI): −0.04 (−0.07, −0.005)). No association was found between other fetal growth endpoints and maternal arsenic at either GW 14 or GW 30. When the data were stratified by sex, authors reported a weak inverse association between maternal arsenic levels (GW 8 and GW 30) and femur length, head circumference, and occipitofrontal diameter in males at GW 14 and GW 30 but not in females (Kippler et al., 2012). In a study based in New Hampshire, maternal urinary arsenic (median (IQR) = 3.1 (1.5–5.5) μg/L) was not associated with fetal growth at 18–22 weeks (e.g., head circumference beta (95% CI): −0.02 mm (−0.05, 0.01)) (Davis et al., 2015).

Summary

High and medium confidence studies covering a range of exposure levels across diverse geographic regions (e.g., United States, China, Bangladesh) and evaluating varying fetal growth outcomes suggest unexplained inconsistency regarding the effect of arsenic on fetal growth. Some studies provide evidence of inverse associations, others provide evidence of positive associations, and others are null. Inverse associations are observed in regions with both high (e.g., Bangladesh, China) and low (e.g., United States) arsenic exposure. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.

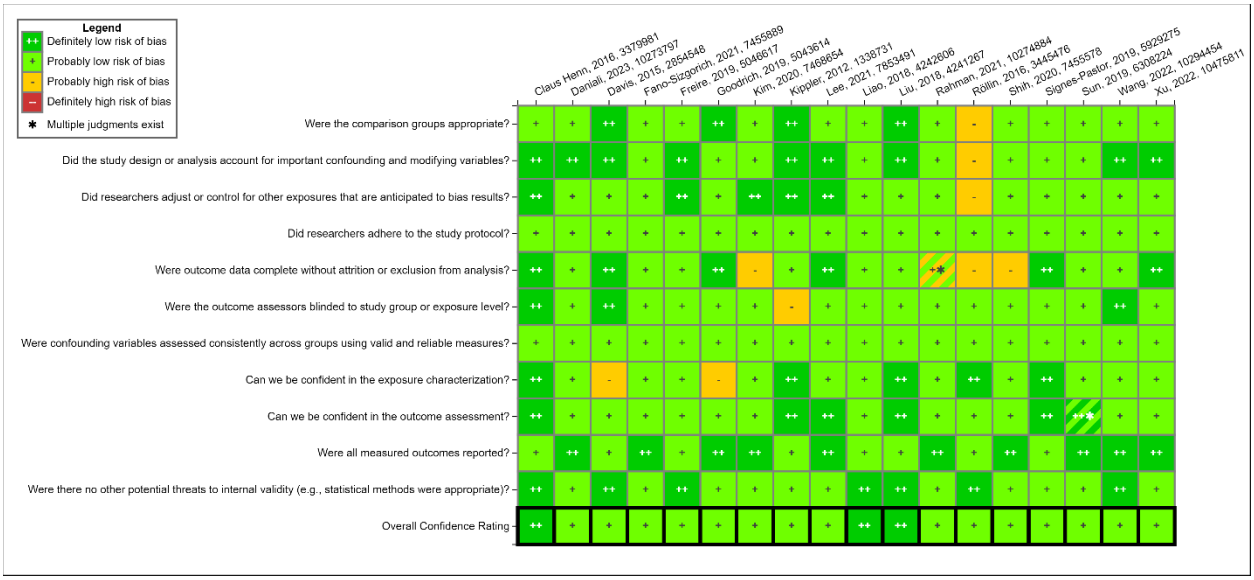
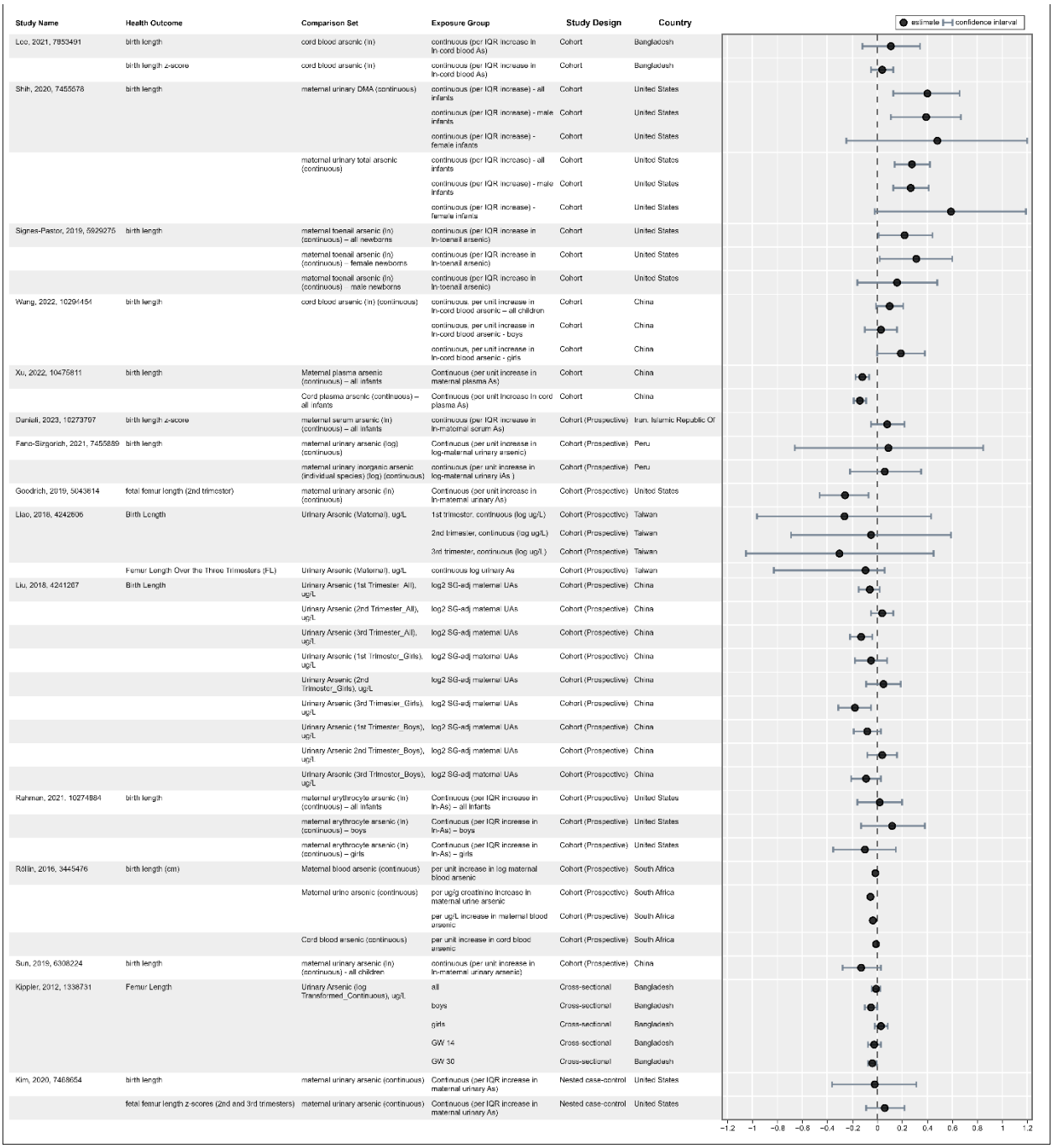
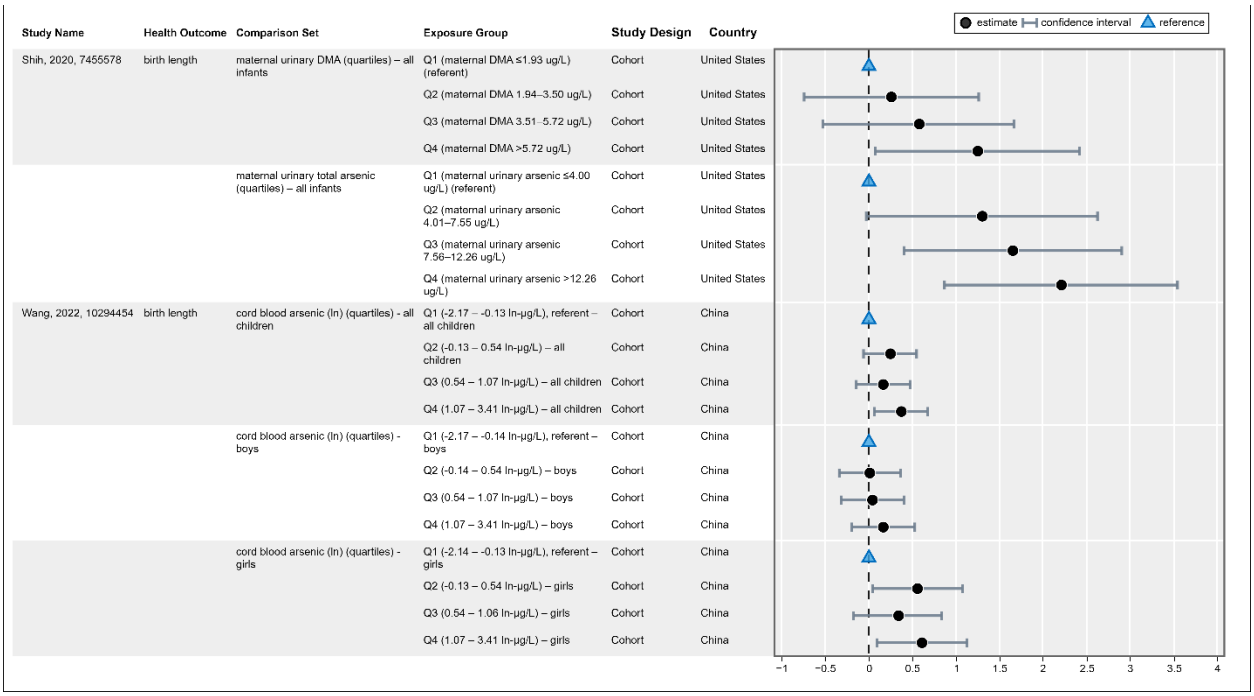


Figure 3-33. Study evaluation ratings for references evaluating fetal growth (see interactive version in HAWC).



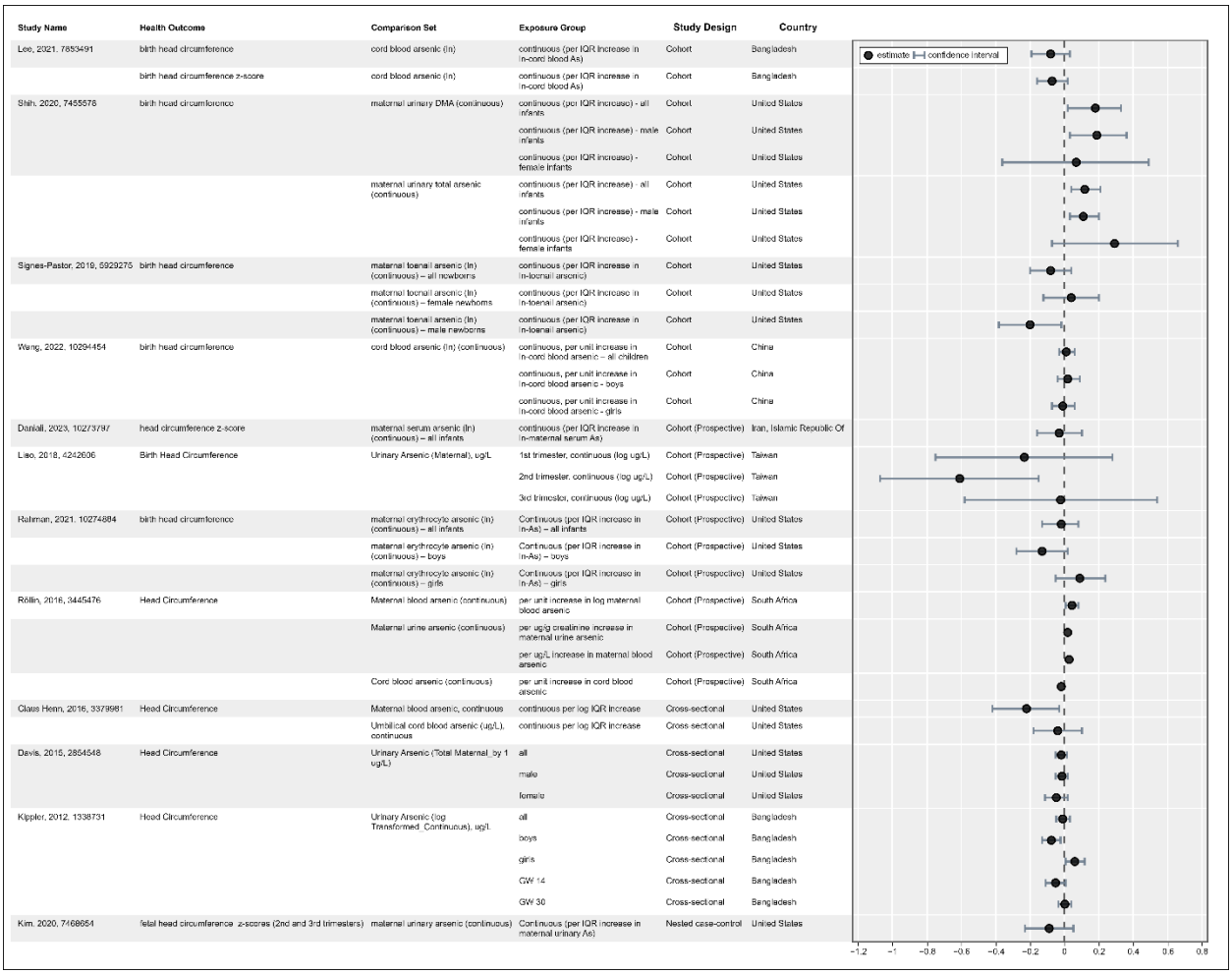
Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Lee, 2021, 7853491	birth length	cord blood arsenic (ln)	continuous (per IQR increase in ln cord blood As)	Cohort	Bangladesh
	birth length z-score	cord blood arsenic (ln)	continuous (per IQR increase in ln-cord blood As)	Cohort	Bangladesh
Shih, 2020, 7455578	birth length	maternal urinary DMA (continuous)	continuous (per IQR increase) - all infants	Cohort	United States
			continuous (per IQR increase) - male infants	Cohort	United States
			continuous (per IQR increase) - female infants	Cohort	United States
		maternal urinary total arsenic (continuous)	continuous (per IQR increase) - all infants	Cohort	United States
			continuous (per IQR increase) - male infants	Cohort	United States
			continuous (per IQR increase) - female infants	Cohort	United States
Signes-Pastor, 2019, 5929275	birth length	maternal toenail arsenic (ln) (continuous) – all newborns	continuous (per IQR increase in ln-toenail arsenic)	Cohort	United States
		maternal toenail arsenic (ln) (continuous) – female newborns	continuous (per IQR increase in ln-toenail arsenic)	Cohort	United States
		maternal toenail arsenic (ln) (continuous) – male newborns	continuous (per IQR increase in ln-toenail arsenic)	Cohort	United States
Wang, 2022, 10294454	birth length	cord blood arsenic (ln) (continuous)	continuous, per unit increase in ln-cord blood arsenic – all children	Cohort	China
			continuous, per unit increase in ln-cord blood arsenic - boys	Cohort	China
			continuous, per unit increase in ln-cord blood arsenic - girls	Cohort	China
Xu, 2022, 10476811	birth length	Maternal plasma arsenic (continuous) – all infants	Continuous (per unit increase in maternal plasma As)	Cohort	China
		Cord plasma arsenic (continuous) – all infants	Continuous (per unit increase in cord plasma As)	Cohort	China
Daniali, 2023, 10273797	birth length z-score	maternal serum arsenic (ln) (continuous) – all infants	continuous (per IQR increase in ln-maternal serum As)	Cohort (Prospective)	Iran, Islamic Republic Of
Fano-Sizgorich, 2021, 7455889	birth length	maternal urinary arsenic (log) (continuous)	Continuous (per unit increase in log-maternal urinary arsenic)	Cohort (Prospective)	Peru
		maternal urinary inorganic arsenic (individual species) (log) (continuous)	continuous (per unit increase in log-maternal urinary iAs)	Cohort (Prospective)	Peru
Goodrich, 2019, 5043614	fetal femur length (2nd trimester)	maternal urinary arsenic (ln) (continuous)	Continuous (per unit increase in ln-maternal urinary As)	Cohort (Prospective)	United States
Liao, 2018, 4242606	Birth Length	Urinary Arsenic (Maternal), ug/L	1st trimester, continuous (log ug/L)	Cohort (Prospective)	Taiwan
			2nd trimester, continuous (log ug/L)	Cohort (Prospective)	Taiwan
			3rd trimester, continuous (log ug/L)	Cohort (Prospective)	Taiwan
	Femur Length Over the Three Trimesters (FL)	Urinary Arsenic (Maternal), ug/L	continuous log urinary As	Cohort (Prospective)	Taiwan
Liu, 2018, 4241267	Birth Length	Urinary Arsenic (1st Trimester_All), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (2nd Trimester_All), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (3rd Trimester_All), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (1st Trimester_Girls), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (2nd Trimester_Girls), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (3rd Trimester_Girls), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (1st Trimester_Boys), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic 2nd Trimester_Boys), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
		Urinary Arsenic (3rd Trimester_Boys), ug/L	log2 SG-adj maternal UAs	Cohort (Prospective)	China
Rahman, 2021, 10274884	birth length	maternal erythrocyte arsenic (ln) (continuous) – all infants	Continuous (per IQR increase in ln-As) – all infants	Cohort (Prospective)	United States
		maternal erythrocyte arsenic (ln) (continuous) – boys	Continuous (per IQR increase in ln-As) – boys	Cohort (Prospective)	United States
		maternal erythrocyte arsenic (ln) (continuous) – girls	Continuous (per IQR increase in ln-As) – girls	Cohort (Prospective)	United States
Röllin, 2016, 3445476	birth length (cm)	Maternal blood arsenic (continuous)	per unit increase in log maternal blood arsenic	Cohort (Prospective)	South Africa
		Maternal urine arsenic (continuous)	per ug/g creatinine increase in maternal urine arsenic	Cohort (Prospective)	South Africa
			per ug/L increase in maternal blood arsenic	Cohort (Prospective)	South Africa
		Cord blood arsenic (continuous)	per unit increase in cord blood arsenic	Cohort (Prospective)	South Africa
Sun, 2019, 6308224	birth length	maternal urinary arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-maternal urinary arsenic)	Cohort (Prospective)	China
Kippler, 2012, 1338731	Femur Length	Urinary Arsenic (log Transformed_Continuous), ug/L	all	Cross-sectional	Bangladesh
			boys	Cross-sectional	Bangladesh
			girls	Cross-sectional	Bangladesh
			GW 14	Cross-sectional	Bangladesh
			GW 30	Cross-sectional	Bangladesh
Kim, 2020, 7468654	birth length	maternal urinary arsenic (continuous)	Continuous (per IQR increase in maternal urinary As)	Nested case-control	United States
	fetal femur length z-scores (2nd and 3rd trimesters)	maternal urinary arsenic (continuous)	Continuous (per IQR increase in maternal urinary As)	Nested case-control	United States

(a) Measures of length, difference measures, biomarkers, continuous exposures



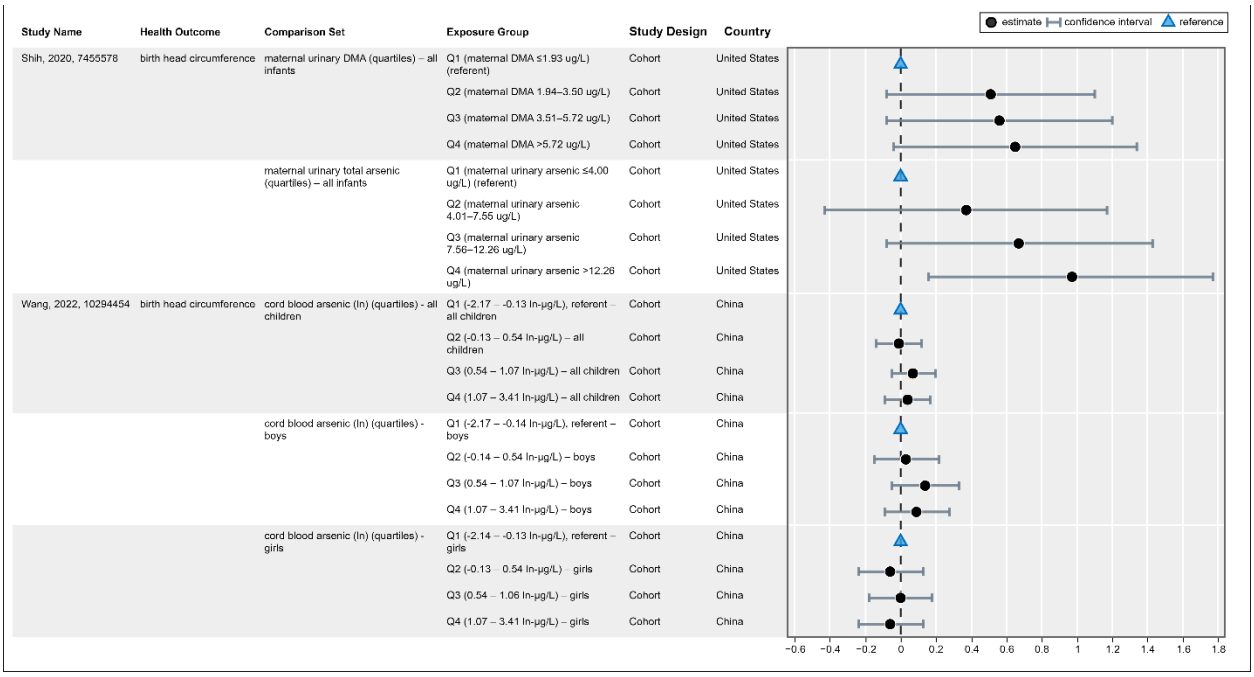
Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Shih, 2020, 7455578	birth length	maternal urinary DMA (quartiles) – all infants	Q1 (maternal DMA ≤1.93 ug/L) (referent)	Cohort	United States
			Q2 (maternal DMA 1.94–3.50 ug/L)	Cohort	United States
			Q3 (maternal DMA 3.51–5.72 ug/L)	Cohort	United States
			Q4 (maternal DMA >5.72 ug/L)	Cohort	United States
		maternal urinary total arsenic (quartiles) – all infants	Q1 (maternal urinary arsenic ≤4.00 ug/L) (referent)	Cohort	United States
			Q2 (maternal urinary arsenic 4.01–7.55 ug/L)	Cohort	United States
			Q3 (maternal urinary arsenic 7.56–12.26 ug/L)	Cohort	United States
			Q4 (maternal urinary arsenic >12.26 ug/L)	Cohort	United States
Wang, 2022, 10294454	birth length	cord blood arsenic (ln) (quartiles) - all children	Q1 (-2.17 – -0.13 ln-µg/L), referent – all children	Cohort	China
			Q2 (-0.13 – 0.54 ln-µg/L) – all children	Cohort	China
			Q3 (0.54 – 1.07 ln-µg/L) – all children	Cohort	China
			Q4 (1.07 – 3.41 ln-µg/L) – all children	Cohort	China
		cord blood arsenic (ln) (quartiles) - boys	Q1 (-2.17 – -0.14 ln-µg/L), referent – boys	Cohort	China
			Q2 (-0.14 – 0.54 ln-µg/L) – boys	Cohort	China
			Q3 (0.54 – 1.07 ln-µg/L) – boys	Cohort	China
			Q4 (1.07 – 3.41 ln-µg/L) – boys	Cohort	China
		cord blood arsenic (ln) (quartiles) - girls	Q1 (-2.14 – -0.13 ln-µg/L), referent – girls	Cohort	China
			Q2 (-0.13 – 0.54 ln-µg/L) – girls	Cohort	China
			Q3 (0.54 – 1.06 ln-µg/L) – girls	Cohort	China
			Q4 (1.07 – 3.41 ln-µg/L) – girls	Cohort	China

(b) Measures of length, difference measures, biomarkers, categorical exposures



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Lee, 2021, 7853491	birth head circumference	cord blood arsenic (ln)	continuous (per IQR increase in ln-cord blood As)	Cohort	Bangladesh
	birth head circumference z-score	cord blood arsenic (ln)	continuous (per IQR increase in ln-cord blood As)	Cohort	Bangladesh
Shih, 2020, 7455576	birth head circumference	maternal urinary DMA (continuous)	continuous (per IQR increase) - all infants	Cohort	United States
			continuous (per IQR increase) - male infants	Cohort	United States
			continuous (per IQR increase) - female infants	Cohort	United States
		maternal urinary total arsenic (continuous)	continuous (per IQR increase) - all infants	Cohort	United States
			continuous (per IQR increase) - male infants	Cohort	United States
			continuous (per IQR increase) - female infants	Cohort	United States
Signes-Pastor, 2019, 5929275	birth head circumference	maternal toenail arsenic (ln) (continuous) – all newborns	continuous (per IQR increase in ln-toenail arsenic)	Cohort	United States
		maternal toenail arsenic (ln) (continuous) – female newborns	continuous (per IQR increase in ln-toenail arsenic)	Cohort	United States
		maternal toenail arsenic (ln) (continuous) – male newborns	continuous (per IQR increase in ln-toenail arsenic)	Cohort	United States
Wang, 2022, 10294454	birth head circumference	cord blood arsenic (ln) (continuous)	continuous, per unit increase in ln-cord blood arsenic – all children	Cohort	China
			continuous, per unit increase in ln-cord blood arsenic - boys	Cohort	China
			continuous, per unit increase in ln-cord blood arsenic - girls	Cohort	China
Daniali, 2023, 10273797	head circumference z-score	maternal serum arsenic (ln) (continuous) – all infants	continuous (per IQR increase in ln-maternal serum As)	Cohort (Prospective)	Iran, Islamic Republic Of
Liao, 2018, 4242606	Birth Head Circumference	Urinary Arsenic (Maternal), ug/L	1st trimester, continuous (log ug/L)	Cohort (Prospective)	Taiwan
			2nd trimester, continuous (log ug/L)	Cohort (Prospective)	Taiwan
			3rd trimester, continuous (log ug/L)	Cohort (Prospective)	Taiwan
Rahman, 2021, 10274884	birth head circumference	maternal erythrocyte arsenic (ln) (continuous) – all infants	Continuous (per IQR increase in ln-As) – all infants	Cohort (Prospective)	United States
		maternal erythrocyte arsenic (ln) (continuous) – boys	Continuous (per IQR increase in ln-As) – boys	Cohort (Prospective)	United States
		maternal erythrocyte arsenic (ln) (continuous) – girls	Continuous (per IQR increase in ln-As) – girls	Cohort (Prospective)	United States
Röllin, 2016, 3445476	Head Circumference	Maternal blood arsenic (continuous)	per unit increase in log maternal blood arsenic	Cohort (Prospective)	South Africa
		Maternal urine arsenic (continuous)	per ug/g creatinine increase in maternal urine arsenic	Cohort (Prospective)	South Africa
			per ug/L increase in maternal blood arsenic	Cohort (Prospective)	South Africa
		Cord blood arsenic (continuous)	per unit increase in cord blood arsenic	Cohort (Prospective)	South Africa
Claus Henn, 2016, 3379981	Head Circumference	Maternal blood arsenic, continuous	continuous per log IQR increase	Cross-sectional	United States
		Umbilical cord blood arsenic (ug/L), continuous	continuous per log IQR increase	Cross-sectional	United States
Davis, 2015, 2854548	Head Circumference	Urinary Arsenic (Total Maternal, by 1 ug/L)	all	Cross-sectional	United States
			male	Cross-sectional	United States
			female	Cross-sectional	United States
Kippler, 2012, 1338731	Head Circumference	Urinary Arsenic (log Transformed, Continuous), ug/L	all	Cross-sectional	Bangladesh
			boys	Cross-sectional	Bangladesh
			girls	Cross-sectional	Bangladesh
			GW 14	Cross-sectional	Bangladesh
			GW 30	Cross-sectional	Bangladesh
Kim, 2020, 7468654	fetal head circumference z-scores (2nd and 3rd trimesters)	maternal urinary arsenic (continuous)	Continuous (per IQR increase in maternal urinary As)	Nested case-control	United States

(c) Head growth, difference measures, biomarkers, continuous exposures



(d) Head growth, difference measures, biomarkers, categorical exposures

Figure 3-34. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and fetal growth (a) measures of length – difference measures, biomarkers, continuous exposures; (b) measures of length, difference measures, biomarkers, categorical exposures; (c) head growth, difference measures, biomarkers, continuous exposures; (d) head growth, difference measures, biomarkers, categorical exposures (see interactive data graphic).

Prematurity

Eighteen *medium* or *high* confidence studies were identified that assessed the association between iAs and preterm birth (defined in most studies as birth prior to GW 37) and/or continuous measures of gestational age (see Figure 3-35 and Figure 3-36) (Yu et al., 2019; Wai et al., 2017; Shih et al., 2020; Röllin et al., 2016; Rahman et al., 2017a; Rahman et al., 2021; Nyanza et al., 2020; Myers et al., 2010; Laine et al., 2015; Karakis et al., 2021; Howe et al., 2020; Freire et al., 2019; Fano-Sizgorich et al., 2021; Bulka et al., 2022; Bloom et al., 2015; Almberg et al., 2017; Ahmad et al., 2001; Aelion et al., 2012). Most of these studies, from the United States, Spain, China, Israel, Peru, and Myanmar, observed no association between arsenic and preterm birth (see Figure 3-36) (Yu et al., 2019; Wai et al., 2017; Shih et al., 2020; Rahman et al., 2021; Myers et al., 2010; Karakis et al., 2021; Howe et al., 2020; Freire et al., 2019; Fano-Sizgorich et al., 2021; Bulka et al., 2022; Bloom et al., 2015). For example, a prospective cohort study by Bloom et al. (2015) analyzed couples enrolled in the Longitudinal Investigation of Fertility and the Environment (LIFE) in the United States and found no association between prepregnancy maternal total urinary arsenic levels (mean (SD) = 17.13 (28.76) µg/L) and gestational age at delivery (beta (95% CI): 2nd tertile vs. ref: −0.40 (−1.43, 0.63); 3rd tertile vs ref: −0.02 (−1.17, 1.13)). Wai et al. (2017) evaluated the association between creatinine-adjusted urinary total arsenic (mean = 74.2 µg/g) measured during the third trimester in 419 women in Myanmar and observed a null association with preterm birth. (OR (95% CI): 1.0 (0.99–1.0))

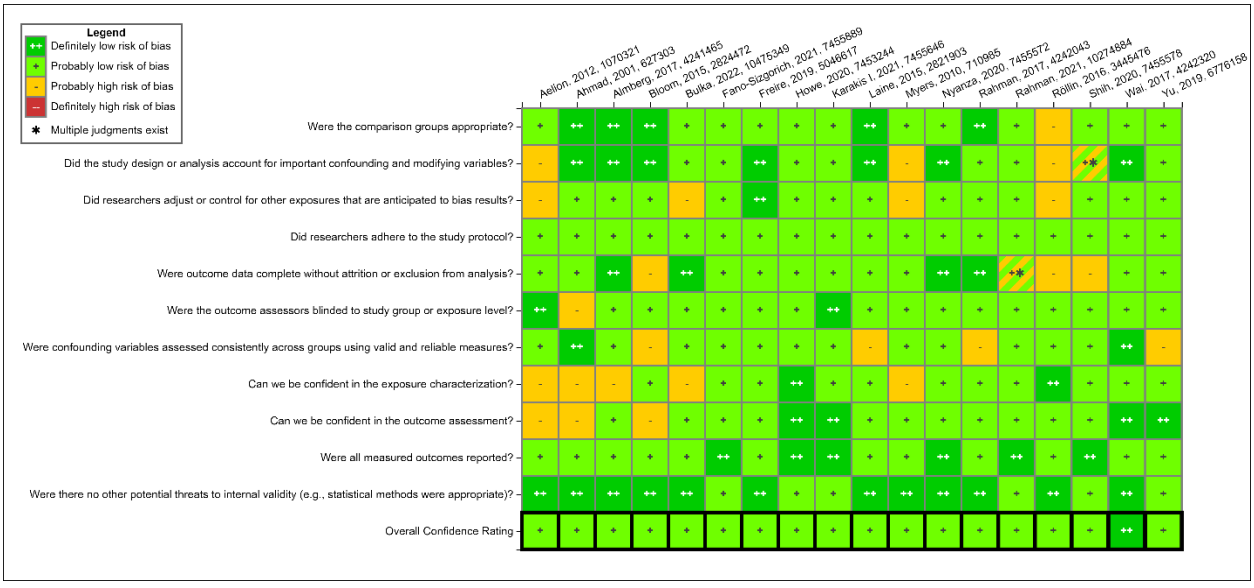


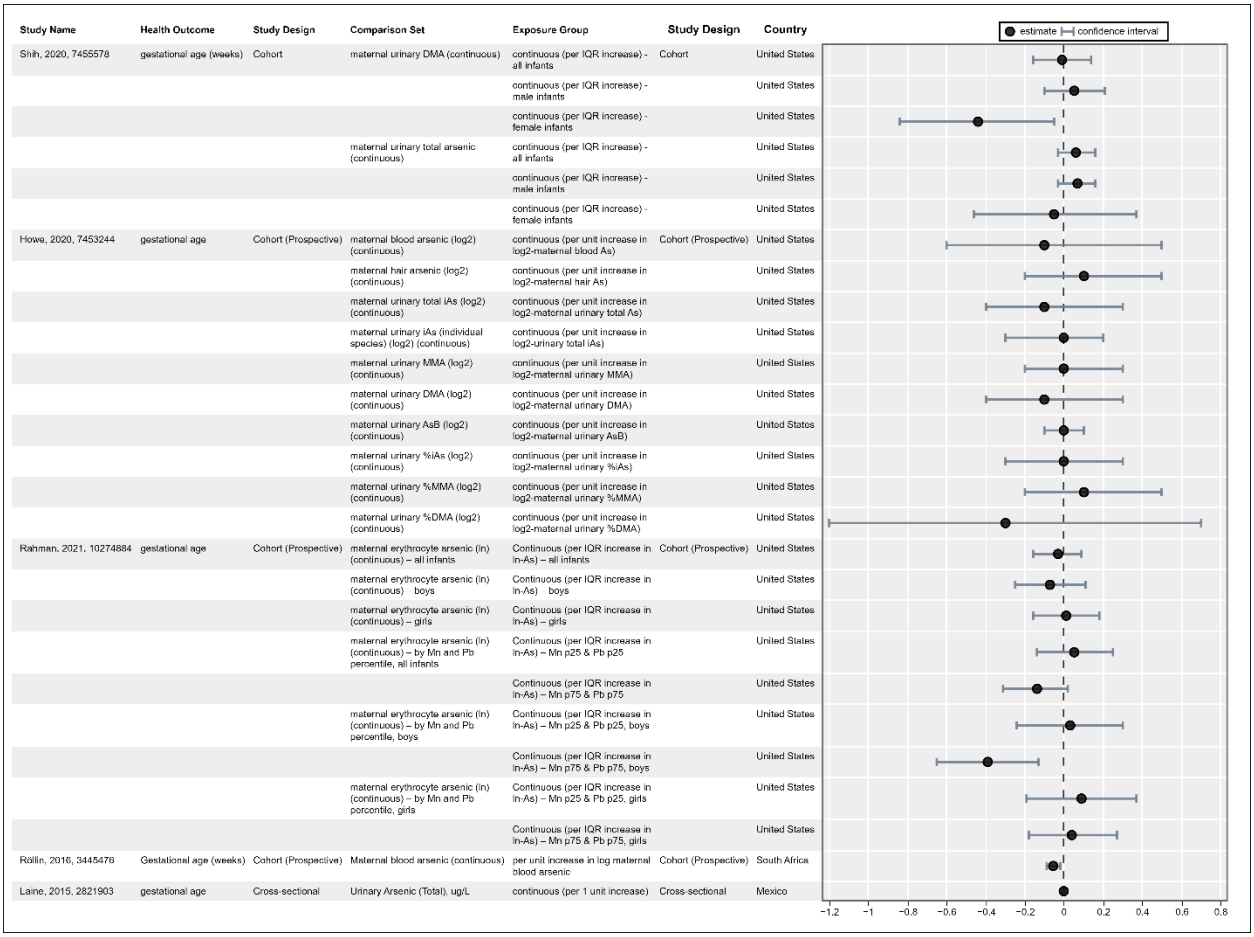
Figure 3-35. Study evaluation ratings for references evaluating prematurity (see interactive version in HAWC).

Conversely, seven studies (Röllin et al., 2016; Rahman et al., 2017a; Nyanza et al., 2020; Laine et al., 2015; Almberg et al., 2017; Ahmad et al., 2001; Aelion et al., 2012) observed

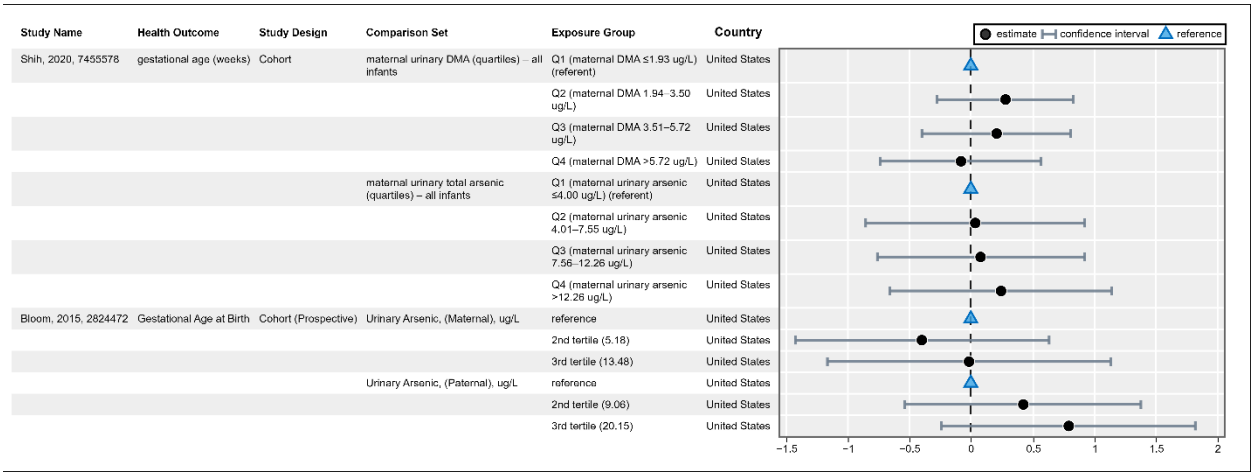
associations with preterm birth using a variety of exposure assessment metrics and across a variety of geographic areas (see Figure 3-36). Two studies conducted in South Africa reported associations with preterm birth at varying exposure levels: Ahmad et al. (2001) observed positive associations with drinking water levels >50 µg/L in a cross-sectional analysis, while a cohort study conducted by Rahman et al. (2017a) reported a positive association with drinking water at much lower levels (median = 2.2 µg/L; RR (95% CI): 1.12 (1.07, 1.18)); results were similar when arsenic measured in toenail samples (median = 1.2 µg/g; RR (95% CI): 1.13 (1.03, 1.24)) was used to assign exposure. In a cohort study based in South Africa, Röllin et al. (2016) reported an inverse association between maternal blood arsenic levels at delivery (geometric mean = 0.96 µg/L) and gestational age (beta (95% CI): −0.054 (−0.087, −0.020)). Finally, a cross-sectional study conducted in Mexico observed an association between urinary iAs levels (mean = 2.1 µg/L) and gestational age at delivery (beta (95% CI): −0.069 weeks (−0.13, −0.0043)) (Laine et al., 2015).

Summary

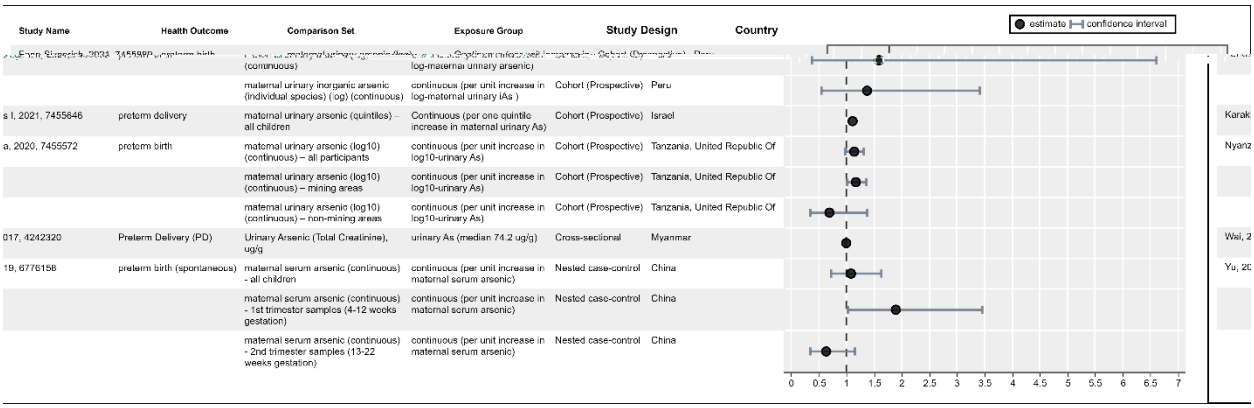
Most studies, covering varying geographic regions, reported no association between arsenic exposure and prematurity. However, seven studies presenting both higher and lower exposure scenarios reported positive associations between arsenic exposure and preterm birth. There is unexplained inconsistency is this set of *medium* and *high* confidence studies. There is some evidence of a dose-response gradient across studies, with some stronger effects documented in areas with higher arsenic exposures [e.g., (Rahman et al., 2017a)] compared with lower arsenic exposures [e.g., (Almberg et al., 2017)]. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.



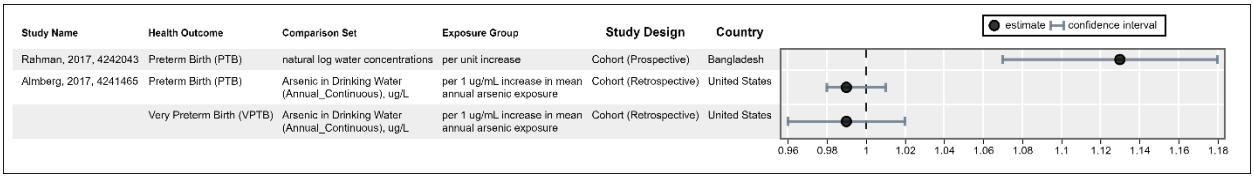
(a) Gestational age, difference measures, biomarkers, continuous exposures



(b) Gestational age, difference measures, biomarkers, categorical exposures



(c) Preterm birth, ratio measures, biomarkers, continuous exposures



(d) Preterm birth, ratio measures, drinking water, continuous exposures

Figure 3-36. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and prematurity (a) gestational age, difference measures, biomarkers, continuous exposures; (b) gestational age, difference measures, biomarkers, categorical exposures; (c) preterm birth, ratio measures, biomarkers, continuous exposures; (d) preterm birth, ratio measures, drinking water, continuous exposures (see interactive data graphic).

Postnatal growth

The evidence for an association between pregnancy iAs exposure and postnatal growth effects is limited to six *medium* or *high* confidence prospective cohort studies (see Figure 3-37), four of which were conducted in Bangladesh (Wai et al., 2020; Saha et al., 2012; Malin Igra et al., 2021; Gardner et al., 2013). The other two studies were conducted in New Hampshire (Muse et al., 2020) and Israel (Karakis et al., 2021).

Two of these studies suggest that prenatal arsenic exposure at a range of concentrations can affect postnatal growth (see Figure 3-38). Wai et al. (2020) observed an inverse association between maternal second or third trimester total urinary arsenic (geometric mean = 50.8 μg/L) and head circumference for age z-score at 1–6 months of age (beta (95% CI): −1.20 (−1.97, −0.42)). By contrast, Muse et al. (2020) documented a positive association between maternal second trimester total urinary arsenic (median = 3.96 μg/L) and length z-score over the first year of life (beta (95% CI): 0.05 (0.00, 0.09)) but an inverse association with length growth rate up to 3.5 months (beta (95% CI): −0.07 cm/mo (−0.12, −0.02). Other studies observed no significant associations between prenatal arsenic exposures at a range of concentrations (median maternal blood arsenic = 4.3 μg/kg; maternal central tendency urinary arsenic = 3.59 μg/L – 80–84 μg/L) and childhood growth outcomes up to age 10 years (Saha et al., 2012; Malin Igra et al., 2021; Karakis et al., 2021; Gardner et al., 2013).

Summary

From a limited evidence base of *medium* or *high* confidence studies, two studies (one in Bangladesh, one in USA) document changes in postnatal growth in relation to prenatal exposure but four studies at overlapping exposure levels document no significant associations. There is unexplained inconsistency in this small evidence base. There is coherence with the evidence for birth weight and some of the evidence for fetal growth. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.

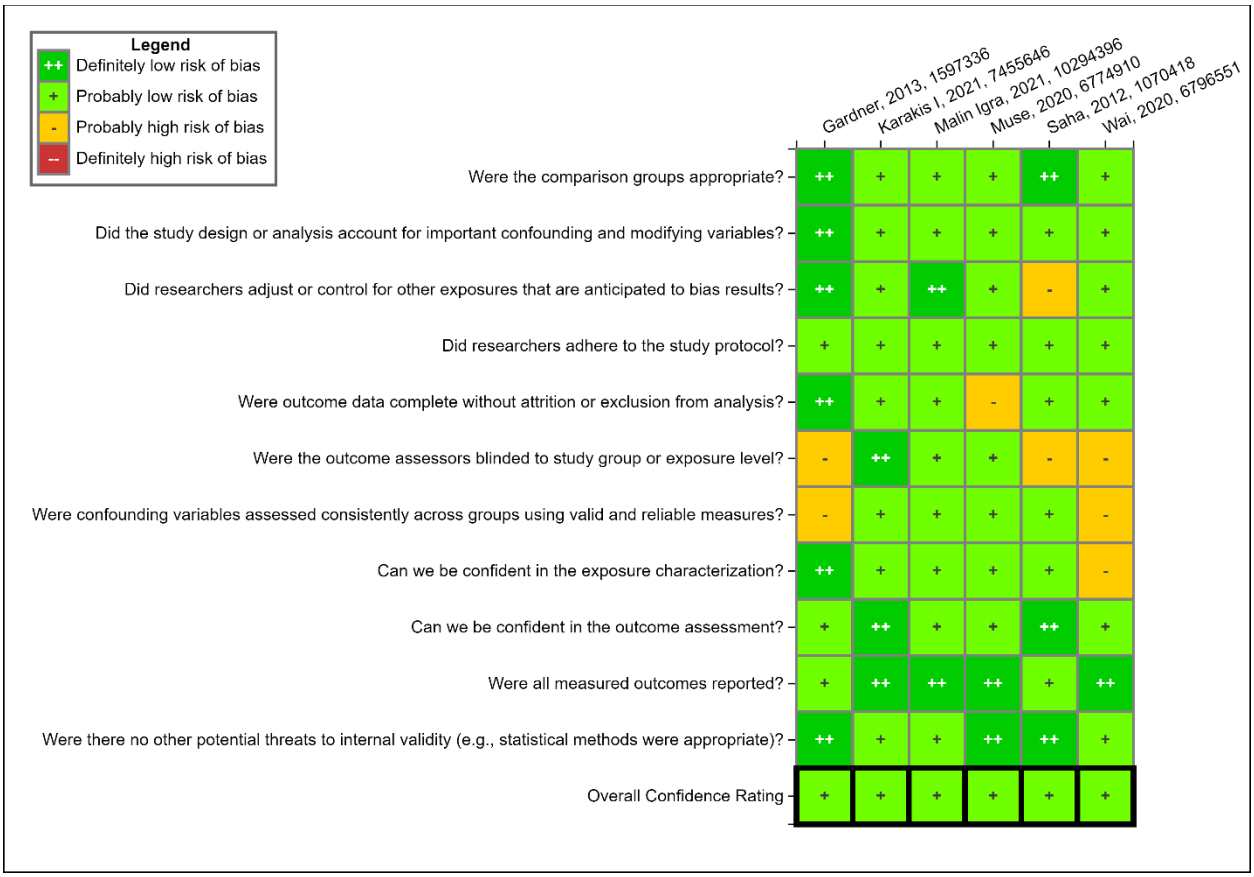
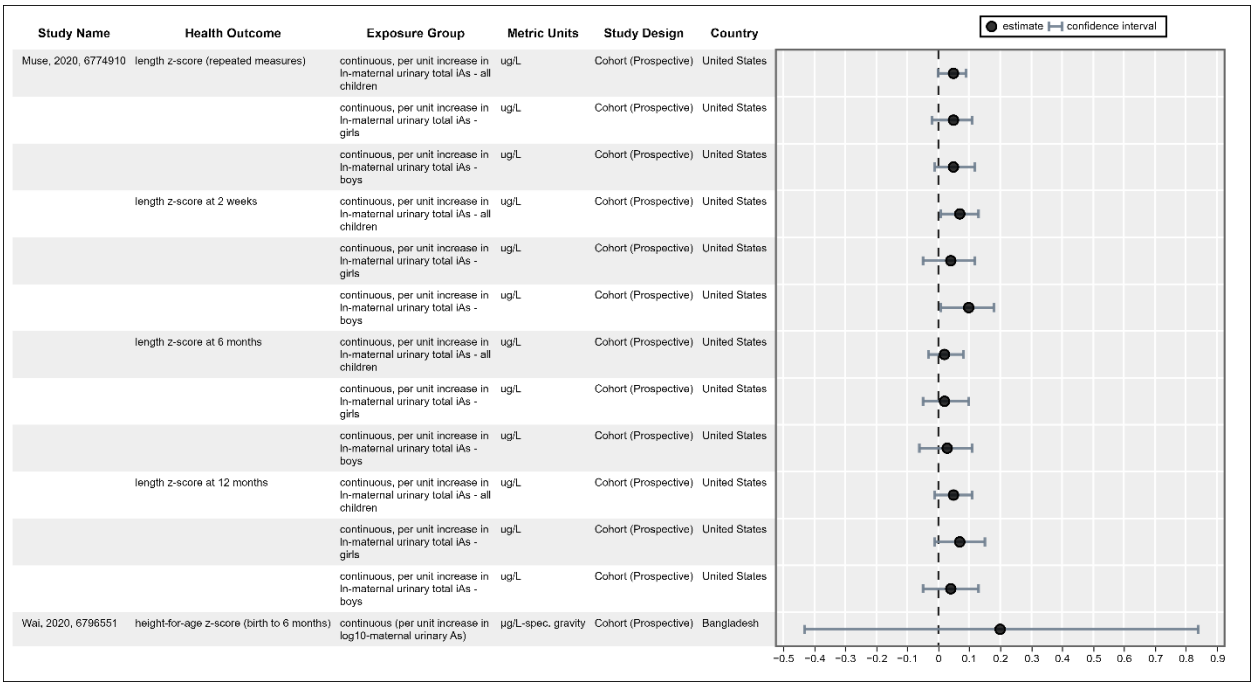
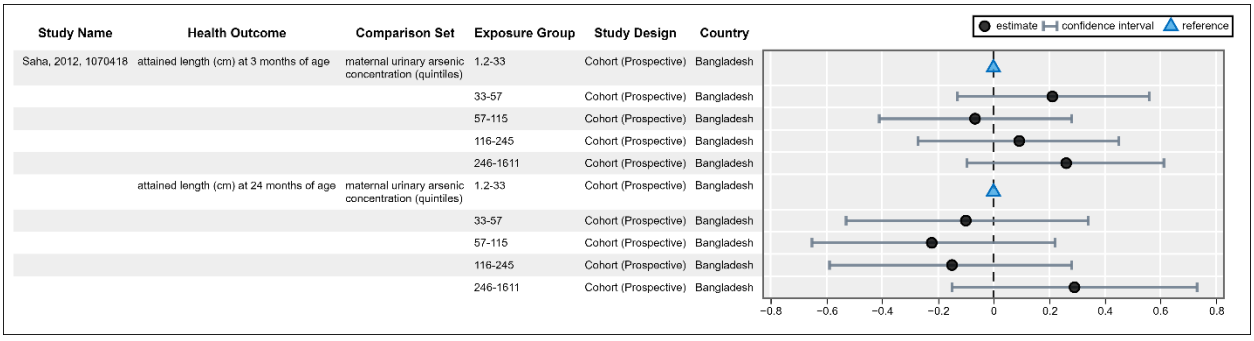


Figure 3-37. Study evaluation ratings for references evaluating postnatal growth (see interactive version in HAWC).



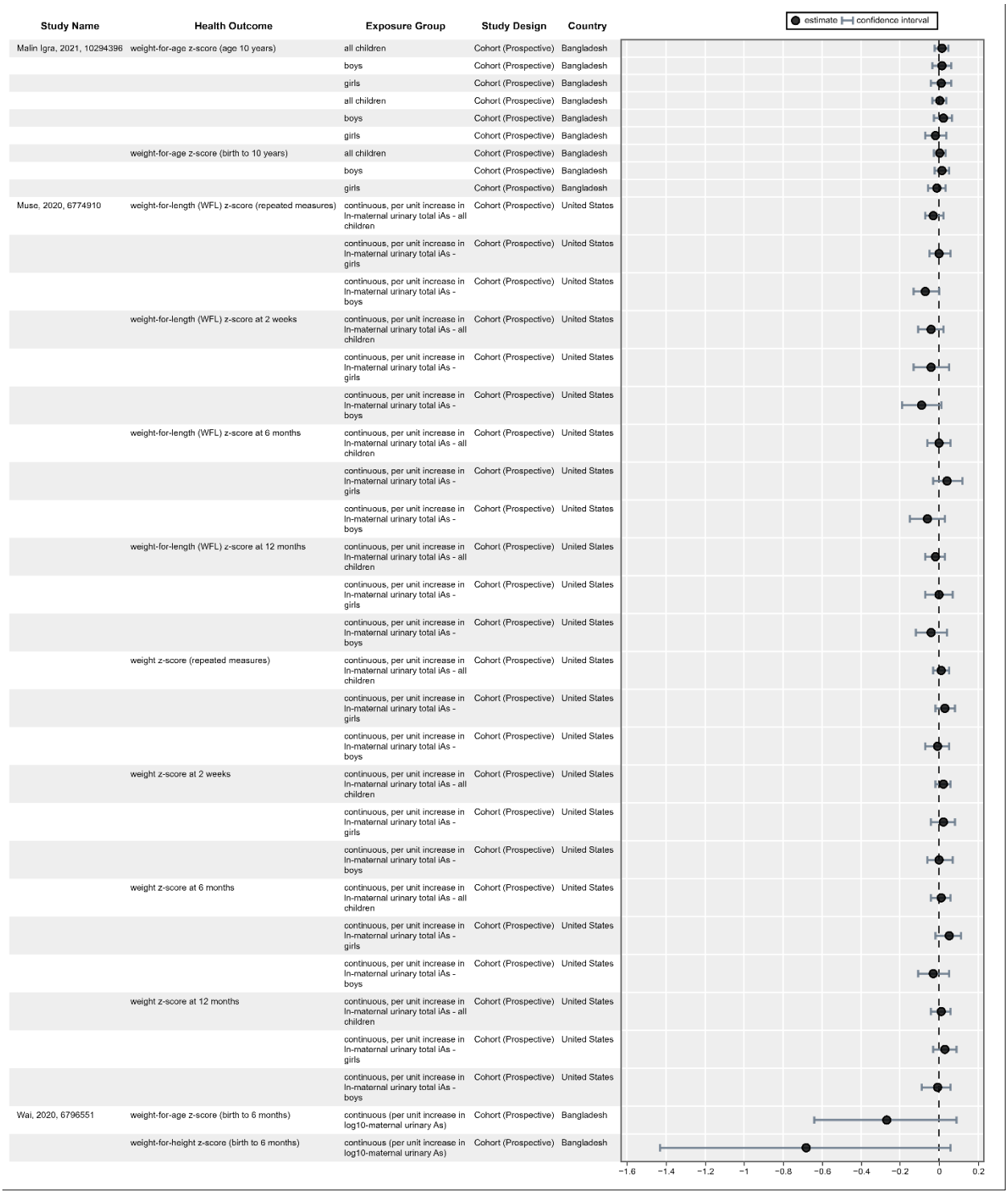
Study Name	Health Outcome	Exposure Group	Metric Units	Study Design	Country
Muse, 2020, 6774910	length z-score (repeated measures)	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L	Cohort (Prospective)	United States
	length z-score at 2 weeks	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L	Cohort (Prospective)	United States
	length z-score at 6 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L	Cohort (Prospective)	United States
	length z-score at 12 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	ug/L	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	ug/L	Cohort (Prospective)	United States
Wai, 2020, 6796551	height-for-age z-score (birth to 6 months)	continuous (per unit increase in log10-maternal urinary As)	µg/L-spec. gravity	Cohort (Prospective)	Bangladesh

(a) Measures of length, difference measures, biomarkers, continuous exposure



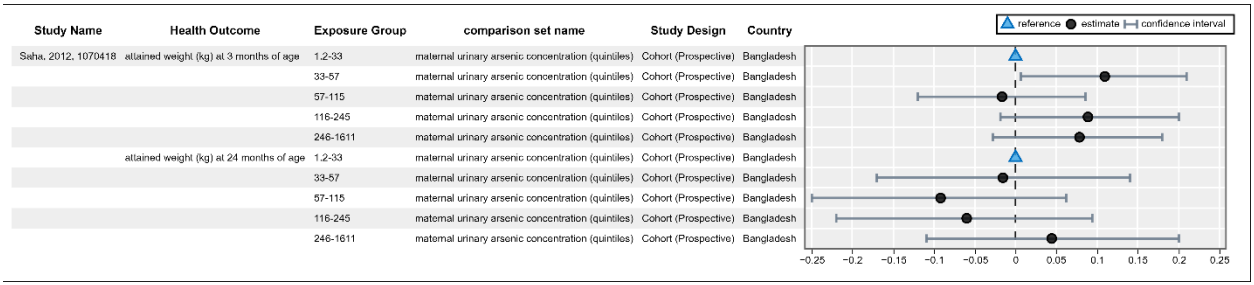
Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Saha, 2012, 1070418	attained length (cm) at 3 months of age	maternal urinary arsenic concentration (quintiles)	1.2-33	Cohort (Prospective)	Bangladesh
			33-57	Cohort (Prospective)	Bangladesh
			57-115	Cohort (Prospective)	Bangladesh
			116-245	Cohort (Prospective)	Bangladesh
			246-1611	Cohort (Prospective)	Bangladesh
	attained length (cm) at 24 months of age	maternal urinary arsenic concentration (quintiles)	1.2-33	Cohort (Prospective)	Bangladesh
			33-57	Cohort (Prospective)	Bangladesh
			57-115	Cohort (Prospective)	Bangladesh
			116-245	Cohort (Prospective)	Bangladesh
			246-1611	Cohort (Prospective)	Bangladesh

(b) Measure of length, difference measure, biomarkers, categorical exposure



Study Name	Health Outcome	Exposure Group	Study Design	Country
Malin Igra, 2021, 10294396	weight-for-age z-score (age 10 years)	all children	Cohort (Prospective)	Bangladesh
		boys	Cohort (Prospective)	Bangladesh
		girls	Cohort (Prospective)	Bangladesh
		all children	Cohort (Prospective)	Bangladesh
		boys	Cohort (Prospective)	Bangladesh
		girls	Cohort (Prospective)	Bangladesh
	weight-for-age z-score (birth to 10 years)	all children	Cohort (Prospective)	Bangladesh
		boys	Cohort (Prospective)	Bangladesh
		girls	Cohort (Prospective)	Bangladesh
Muse, 2020, 6774910	weight-for-length (WFL) z-score (repeated measures)	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight-for-length (WFL) z-score at 2 weeks	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight-for-length (WFL) z-score at 6 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight-for-length (WFL) z-score at 12 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight z-score (repeated measures)	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight z-score at 2 weeks	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight z-score at 6 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
	weight z-score at 12 months	continuous, per unit increase in ln-maternal urinary total iAs - all children	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - girls	Cohort (Prospective)	United States
		continuous, per unit increase in ln-maternal urinary total iAs - boys	Cohort (Prospective)	United States
Wai, 2020, 6796551	weight-for-age z-score (birth to 6 months)	continuous (per unit increase in log10-maternal urinary As)	Cohort (Prospective)	Bangladesh
	weight-for-height z-score (birth to 6 months)	continuous (per unit increase in log10-maternal urinary As)	Cohort (Prospective)	Bangladesh

(c) Measures of weight, difference measures, biomarkers, continuous exposure



(d) Measures of weight, difference measures, biomarkers, continuous exposure

Figure 3-38. Thumbnail schematic of epidemiological studies addressing the association between inorganic arsenic exposure and postnatal growth (a) measures of length, difference measures, biomarkers, continuous exposures; (b) measure of length, difference measure, biomarkers, categorical exposures; (c) measures of weight, difference measures, biomarkers, continuous exposures; (d) measures of weight, difference measure, biomarkers, categorical exposures (see interactive data graphic).

Mechanistic Observations and Biological Plausibility

Arsenic exposure could affect fetal or infant development by damaging the fetus directly or by impairing the function of the placenta and thereby negatively affecting fetal growth and development. Whether maternal iAs is taken up by the placenta (Hanlon and Ferm, 1987) and the fetus (Hood et al., 1988; Gerber et al., 1982) is unclear. Human studies, such as that by Huyck et al. (2007) demonstrated uptake of arsenic by the fetus. A few studies have evaluated the mechanism of arsenic on the placenta. Using a human extravillous trophoblast cell line, Li and Loch-Caruso (2007) found that placental trophoblast migration is reduced by arsenic, an effect that could cause poor placental development. Two studies by the same group showed that arsenic impaired vasculogenesis of the placenta in pregnant mice, which could reduce nutritional uptake by the fetus and lead to reduced birth weight (Coffin et al., 2006; He et al., 2007). Remy et al. (2014) found that arsenic was associated with upregulation of soluble fms-like tyrosine kinase-1 (sFLT1), a protein that inhibits placental angiogenesis, in human female cord blood. The authors of this study also found a correlation between arsenic exposure and increased expression of genes related to DNA damage and oxidative stress in cord blood, (e.g., *GPX7, SNCA, YBX1*, *BRCA1, MMP2, MMP9, PEMT, S100A12, SELK, TAT, VNN1*and *MYC*)but found no association between these effects and fetal, newborn, and infant health outcomes. Fei et al. (2013) found that maternal arsenic exposure in humans was correlated with placental upregulation of *aquaporin 9* (*AQP9*), which encodes a membrane transporter that contributes to arsenic uptake. A related decrease in *ENPP2* was associated with decrease in birth weight.

Studies using human placentas or placental cell lines suggest that arsenic might increase oxidative stress and cytokine expression, including increased intracellular H_2O_2 (Massrieh et al., 2006) and increased expression of *TNFα* and *IFN-γ* (Ahmed et al., 2011). Oxidative stress is an established mode of action for arsenic and is described in detail in Appendix A of the iAs Protocol.

Another study showed that arsenic exposure causes increases in *TNF*-related inflammatory proteins in cord blood (Bailey et al., 2014). As a whole, the studies described here suggest a variety of pathways by which arsenic exposure could affect the placenta in ways that reduce fetal growth and lead to low birth weight.

In addition, researchers have identified direct effects of arsenic on mouse embryonic cells that plausibly could lead to reduced fetal growth. Arsenic treatment of mouse embryonic cells induced oxidative stress (Ren et al., 2014; Singh et al., 2010; Zhang et al., 2010), cell death, and DNA damage (Mirkes and Little, 1998). That these inflammatory and oxidative stress effects impair the ability of the fetus and infant to thrive is plausible. Specific pathways by which arsenic-induced stress and DNA damage could affect prenatal and postnatal growth are not clear.

Because iAs metabolism appears to increase in humans in late pregnancy and arsenic is not passed readily through breast milk, arsenic exposure during the perinatal period might not be associated with infant death via direct toxic mechanisms (Fängström et al., 2008; Concha et al., 1998). In a prospective cohort study in Bangladesh, Rahman et al. (2011) found increased risk of diarrhea, lower respiratory tract infections, and severe lower respiratory tract infections (maternal reports) among infants born to mothers in the highest quintiles of urinary arsenic concentration (>261 μg/L) in pregnancy compared with those with low urinary arsenic (<261 μg/L). In a study in the United States (New Hampshire), Farzan et al. (2013b) also found increased risk of infections (diarrhea, lower respiratory tract) in infants born to mothers with higher urinary arsenic. Although actual infant deaths from diarrhea or respiratory infections are comparatively uncommon in the United States, they are major causes of infant mortality worldwide (Liu-Mares et al., 2013). There is ample evidence that generation of reactive oxygen species (ROS) and oxidative stress are MOAs involved in arsenic toxicity as there is no one "established" MOA for iAs. For more information see Appendix A of the iAs protocol).

Inorganic arsenic exposure may affect fetal or infant development by damaging the fetus directly or indirectly by impairing placental function and thereby negatively affecting fetal growth and development. Human fetal arsenic uptake has been evaluated, as an example (Huyck et al., 2007) showed that increased arsenic measured in maternal hair negatively correlated with birth weight in a Bangladeshi population exposed to > 50 μg/L arsenic in drinking water. Li et al., (2007) showed a dose-dependent decrease in placental trophoblast migration in response to 0, 0.625, 1.25, or 2.5 μM arsenic. Decreases in placental trophoblast migration could result in poor placental development. Arsenic has also been found to inhibit placental angiogenesis (Remy et al., 2014). Maternal arsenic exposure in humans is correlated with placental upregulation of *aquaporin 9* (*AQP9*), which encodes a membrane transporter that contributes to arsenic uptake. A related decrease in *ENPP2,* which stimulates angiogenesis, was associated with decrease in birth weight (Fei et al., 2013).

Evidence in rodent studies support the epidemiological observations of a correlation between arsenic exposure and low birth weight; as an example, pregnant mice exposed to arsenic

experienced impaired placental vasculogenesis, which could reduce nutritional uptake by the fetus and lead to reduced birth weight (Coffin et al., 2006; He et al., 2007). In addition, researchers have identified direct effects of arsenic on mouse embryonic cells that plausibly could lead to reduced fetal growth. Arsenic treatment of mouse embryonic cells induced oxidative stress (Ren et al., 2014; Singh et al., 2010; Zhang et al., 2010), cell death, and DNA damage (Mirkes and Little, 1998). That these inflammatory and oxidative stress effects impair the ability of the fetus and infant to thrive is plausible. The above studies provide evidence of biologically plausible pathways by which arsenic exposure could affect the placenta in ways that would result in reduced fetal growth and lead to low birth weight.

Risk Modifiers

A review of the epidemiological studies discussed in this section, along with studies identified from a targeted literature search (see Section 3.10 of iAs Protocol), suggest the following as potential modifying factors that may affect the risk of arsenic-associated adverse fetal, newborn, and infant health outcomes (see Table 3-6). (Note that this section is not a comprehensive list of risk modifiers but rather provides selected examples):

- **Sex:** Information is inconclusive regarding whether males or females are more susceptible to arsenic-induced morbidity or mortality during pregnancy. Some studies suggest increased susceptibility among males for certain outcomes (Signes-Pastor et al., 2019a; Luo et al., 2017; Kippler et al., 2012), while others suggest increased susceptibility among females for other outcomes (Signes-Pastor et al., 2019a; Liu et al., 2018).

- **Nutritional status:** Some evidence suggests that the impact of arsenic on infant birth weight is stronger among women who are B12 deficient or who have hyperhomocysteinemia (Clark et al., 2022).

- **Smoking:** Some evidence suggests that the impact of arsenic on birth weight and birth weight is stronger among smokers (Bloom et al., 2016).

- **Maternal prepregnancy weight:** Some evidence suggests that the impact of arsenic on birth weight and fetal growth parameters is stronger for women who are overweight/obese (Gilbert-Diamond et al., 2016).

Table 3-6. Risk modifiers for fetal, newborn, and infant health outcomes (selected study examples)

Risk modifiers	References	Finding	Population, exposure level
Sex	Kippler et al. (2012)	Stronger associations with fetal size among males	Bangladesh, 168 µg/L (prenatal mean maternal urine)
	Luo et al. (2017)	Stronger associations with birth weight among males	United States, ~0.4 µg/L (prenatal median maternal blood)
	Liu et al. (2018)	Stronger associations with birth weight and birth length in females	China, 20–21 µg/L (prenatal median maternal SG-adjusted urine)
	Signes-Pastor et al. (2019a)	Stronger associations with birth weight and birth length in females; stronger associations with head circumference among males	United States, 0.05 µg/g (postnatal median maternal toenail)
Nutritional status	Clark et al. (2022)	Stronger associations for birth weight among infants born to women who were B12 deficient or with hyperhomocysteinemia	Mexico, 1.3 µg/L (maternal mean SG-adjusted urinary inorganic arsenic at delivery)
Smoking	Bloom et al. (2016)	Elevated arsenic associated with lower birth weight and shorter birth length among smokers only	Romania, 4.11 µg/L (mean drinking water)
Maternal prepregnancy weight	Gilbert-Diamond et al. (2016)	Elevated arsenic associated with lower ponderal index in infants of overweight/obese mothers. Elevated arsenic associated with lower birth weight among females born to overweight/obese mothers.	United States, 0.3 µg/L (median urinary arsenic)

Evidence Judgment

The currently available **evidence indicates** that iAs exposure likely causes adverse fetal, newborn, and infant health outcomes in humans (see Table 3-7) given sufficient exposure

conditions.[22] This conclusion is based on epidemiological studies at a range of exposure levels (including <100 µg/L, as well as <20 µg/L) demonstrating associations between iAs exposure and increased fetal and infant mortality, changes in fetal and postnatal growth, length of gestation or birth weight across diverse geographic areas. (Supplemental figures of results from studies documenting adverse effects from exposure to inorganic arsenic in drinking water at concentrations less than or equal to 100 µg/L, as described in 1.6.3, are available in Appendix B.5.)

Overall, there is *moderate* evidence for an association between arsenic exposure and fetal and infant mortality, based on 13 *medium* or *high* confidence studies. The strongest evidence supporting an association between iAs exposure and these outcomes is from cohort and cross-sectional studies conducted in Bangladesh and India, where iAs levels in drinking water wells commonly exceeded 200 µg/L [e.g., (Ahmad et al., 2001; Milton et al., 2005; Rahman et al., 2007; Rahman et al., 2010; Shih et al., 2017; von Ehrenstein et al., 2006)]. Ecological studies in Bangladesh and China also provide supporting evidence for the association between iAs exposure and fetal and infant mortality, including at lower levels of exposure (e.g., <100 µg/L in drinking water) (Cherry et al., 2010; Myers et al., 2010; Cherry et al., 2008). Overall, there is general *consistency* within the evidence base across several study types (cross-sectional, cohort, ecological), geographic regions (China, Bangladesh, India, and Tanzania), and outcome metrics (spontaneous abortion, stillbirth, infant death, neonatal death, and post-neonatal death). A *dose-response gradient* was observed within some [e.g., (Cherry et al., 2008; Cherry et al., 2010)] but not all studies. Some other studies suggested possible dose-response gradients, but these were attenuated at higher exposure levels [e.g., (Rahman et al., 2007; Rahman et al., 2010; Milton et al., 2005)]. There is also some evidence of a *dose-response gradient* across studies based on stronger effects from higher exposure regions [e.g., (Shih et al., 2017)] compared with lower exposure regions (Louis et al., 2017).

There is also *moderate* evidence for an association between arsenic exposure and birth weight. Thirty-five *medium* or *high* confidence studies across diverse geographic regions (e.g., China, United States, Chile, Bangladesh) representing a range of exposure levels and utilizing a variety of exposure assessment methods provide general *consistency* regarding inverse and suggestive inverse associations between iAs and birth weight. This association may be mediated by gestational age (see Section on *Prematurity*, below). There is *coherence* with some of the evidence for fetal growth, postnatal growth, and prematurity.

There is *slight* evidence for an association between arsenic exposure and fetal growth, based on twenty *medium* or *high* confidence studies covering diverse geographic regions (e.g., United States, China, Bangladesh). Studies using a variety of exposure assessment methods and covering a range of overlapping exposure levels had *unexplained inconsistency* with positive [e.g., (Signes-Pastor et al., 2019a; Shih et al., 2020)] and inverse [e.g., (Liu et al., 2018; Liao et al., 2018;

[22]The term, "sufficient exposure conditions," is discussed and defined for the identified health effects in the dose-response analysis in Section 4.

Goodrich et al., 2019)] associations with a variety of fetal growth parameters. There is *coherence* with the evidence for birth weight and some of the evidence for postnatal growth and prematurity.

There is *slight* evidence for an association between arsenic and prematurity. Eighteen *medium* or *high* confidence cohort and cross-sectional studies evaluated the association between arsenic exposure (evaluated using a range of exposure assessment approaches) and prematurity. Most studies reported no association, but seven studies representing both higher and lower exposure scenarios reported positive associations (Röllin et al., 2016; Rahman et al., 2017a; Nyanza et al., 2020; Laine et al., 2015; Almberg et al., 2017; Ahmad et al., 2001; Aelion et al., 2012). There in *unexplained inconsistency* in these studies covering overlapping arsenic exposure levels. There is some evidence of a *dose-response gradient* across studies, with some stronger effects documented in areas with higher arsenic exposures [e.g., (Rahman et al., 2017a)] compared with lower arsenic exposures [e.g., (Almberg et al., 2017)].

There is also *slight* evidence for the association between prenatal arsenic exposure and postnatal growth based on significant associations in two (Wai et al., 2020; Muse et al., 2020) of six *medium* or *high* confidence studies. There is *unexplained inconsistency* in this small evidence base. There is *coherence* with the evidence for birth weight and some of the evidence for fetal growth.

There is some evidence regarding potential modifying factors (sex, nutritional status, smoking, and maternal prepregnancy weight) that may impact the association between arsenic and fetal, newborn, and infant health outcomes.

Overall, the currently available epidemiologic **evidence indicates** that iAs likely causes adverse fetal, newborn, and infant health outcomes in humans given sufficient exposure conditions. This conclusion is based on epidemiological studies at a variety of exposure levels (including <100 μg/L (and also including <20 μg/L) showing associations between iAs exposure and adverse fetal, newborn, and infant health outcomes. Therefore, fetal, newborn, and infant health outcomes will be considered for dose-response analysis (see Section 4.4).

Table 3-7. Evidence profile table for epidemiological evidence on iAs and fetal, newborn, and infant health outcomes

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
Studies	**Summary of key findings**	**Factors that increase certainty**	**Factors that decrease certainty**	**Evidence synthesis judgment(s)**
Fetal & infant mortality 13 *medium* or *high* confidence studies	The strongest evidence of positive associations comes from largely consistent cohort and cross-sectional studies conducted in Bangladesh and India, where iAs levels in drinking water wells commonly exceed 200 µg/L. Other studies, including in other regions of the world, provide evidence at lower levels of exposure (e.g., <100 µg/L)	• Studies are *medium* or *high* confidence • *Consistency* – across geographic regions, study types, and outcome metrics • *Dose-response gradient* – for some but not all studies	• Imprecision – some studies with large confidence intervals including the null	⊕⊕⊙ *Moderate*
Birth weight 36 *medium* or *high* confidence studies	Studies across diverse geographic regions representing a range of exposure levels and utilizing a variety of exposure assessment methods provide generally consistent results indicating statistically significant and nonsignificant inverse associations between iAs and birth weight.	• Studies are *medium* or *high* confidence. • *Consistency* – across geographic regions and study types • *Coherence* – with some evidence from fetal growth, prematurity, and postnatal growth evidence	• Imprecision – some studies with large confidence intervals including the null	⊕⊕⊙ *Moderate*

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
Studies	**Summary of key findings**	**Factors that increase certainty**	**Factors that decrease certainty**	**Evidence synthesis judgment(s)**
Fetal growth 24 *medium* or *high* confidence studies	Studies from diverse geographic regions covering overlapping exposure levels provide conflicting results for a variety of fetal growth parameters. Inverse associations are observed in regions with both high (e.g., Bangladesh, China) and low (e.g., United States) arsenic exposure.	• Studies are *medium* or *high* confidence. • *Coherence* – with evidence for birth weight and some of the evidence for postnatal growth and prematurity	• *Unexplained inconsistency* – between studies with overlapping exposure levels • Imprecision – some studies with large confidence intervals including the null	⊕⊙⊙ *Slight*
Prematurity 18 *medium* or *high* confidence studies	Most studies reported no association, but seven studies representing both higher and lower exposure scenarios reported significant positive associations.	• Studies are *medium* or *high* confidence. • *Dose-response gradient* – some evidence of stronger effects in areas with higher arsenic exposures compared with lower arsenic exposures	• *Unexplained inconsistency* – between studies with overlapping exposure levels • Imprecision – some studies with large confidence intervals including the null	⊕⊙⊙ *Slight*
Postnatal growth 6 *medium* or *high* confidence studies	Two studies (one in Bangladesh, one in USA) document changes in postnatal growth in relation to prenatal exposure but four studies at overlapping exposure levels document no significant associations.	• Studies are *medium* or *high* confidence. • *Coherence* – with birth weight and some fetal growth evidence	• *Unexplained inconsistency* – between studies with overlapping exposure levels • *Imprecision* – some studies with large confidence intervals including the null	⊕⊙⊙ *Slight*

3.2.4. Neurodevelopmental Effects

Database Overview

In 2013, the NRC concluded that low-to-moderate levels of inorganic arsenic (iAs) are associated with neurological deficits based on evidence from both human and animal studies (NRC, 2013). As a result, evaluation of neurodevelopmental toxicity was categorized as a priority outcome by the NRC and recommended for consideration for dose-response analysis in the IRIS Toxicological Review. As described in the protocol (link provided in Appendix A) and supported by the (NASEM, 2019), the assessment focuses on the epidemiological evidence to highlight those studies in humans that best support dose-response analysis. On the basis of the analysis of epidemiological evidence, the strength of evidence was considered "moderate" which corresponds to an evidence judgment that the currently available **evidence indicates** that iAs likely causes neurodevelopmental effects in humans.

There are 85 studies that report on the association between arsenic exposures and neurodevelopmental effects. The publications underwent study evaluation, and 63 of the studies were considered *medium* or *high* confidence. Of the remaining studies, 19 were considered low confidence or uninformative due to limitations as noted in HAWC (see HAWC), and three identified in the 2022 search update were not considered further due to lack of hazard and/or dose-response utility (see Section 1.6.1). Citations of studies broken down by confidence level, type of neurodevelopmental outcome, and studies from the post-2019 literature updates that were not further considered in the assessment can be accessed via the interactive HAWC literature tag-tree visual presented in Figure 3-39. Because of the abundance of the evidence base, the subsequent synthesis is focused on the *medium* and *high* confidence studies as described in the protocol and supported by the NASEM (NASEM, 2019). Mechanistic studies and studies that evaluated various risk modifiers (e.g., life stage, sex, and environmental co-exposures) also provide some evidence that early-life exposure to arsenic and co-exposures to lead might increase susceptibility to arsenic-associated neurodevelopmental effects.

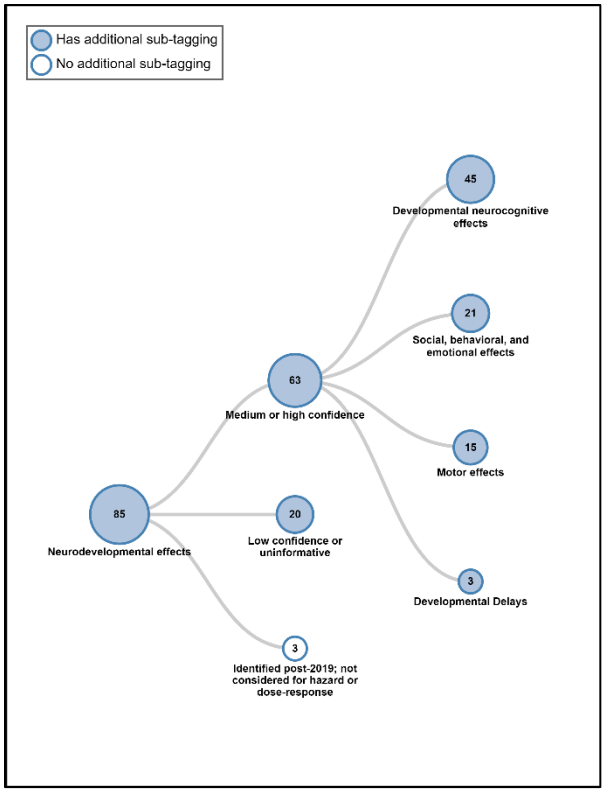


Figure 3-39. Literature tree for epidemiological studies assessing neurodevelopmental effects (see interactive version in HAWC).

Evidence from Epidemiological Studies

This section summarizes the epidemiological studies that evaluated an association between iAs exposure and neurodevelopmental outcomes. Key considerations in evaluating these studies are reviewed in Section 1.6.2. Because of the extended timeline of brain development, critical windows of exposure to arsenic extend from pregnancy through adolescence (Rice and Barone, 2000). Evidence indicates that arsenic accumulates in the brain (Sánchez-Peña et al., 2010). Additional considerations regarding potential susceptibility based on arsenic metabolism and distribution are reviewed in Section 1.5.1. The information below is organized by type of neurodevelopmental effect: (1) developmental neurocognitive effects; (2) social, behavioral, and emotional effects; (3) motor effects, and (4) general/crosscutting developmental delays.

Developmental neurocognitive effects

Forty-five epidemiological studies assessed an association between arsenic and developmental neurocognitive function in children and classified as *medium* or *high* confidence (see Figure 3-40). The studies primarily evaluated cognition using tests to measure learning, short- and long-term memory, verbal comprehension, perceptual reasoning, processing speed, executive function, and visuospatial function.

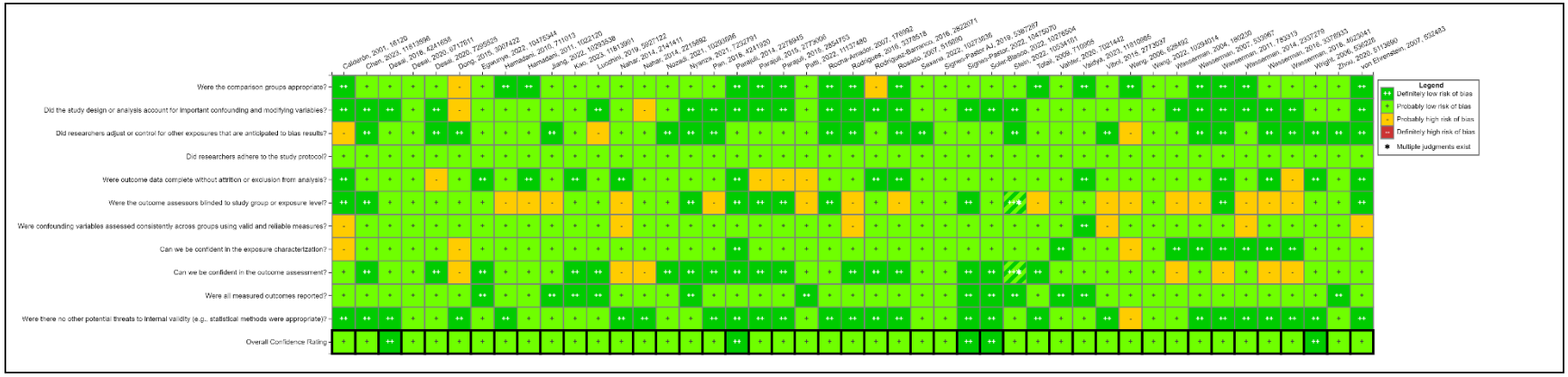


Figure 3-40. Study evaluation ratings for references evaluating developmental neurocognitive effects (see [interactive version in HAWC]).

Cohort and case-control studies

Seventeen *medium* or *high* confidence cohort and case-control studies examined the association between arsenic exposure and developmental neurocognitive effects in young children and adolescents in Taiwan (Jiang et al., 2022), China (Wang et al., 2022b; Chen et al., 2023) , Bangladesh (Wasserman et al., 2016; Vahter et al., 2020; Tofail et al., 2009; Rodrigues et al., 2016; Hamadani et al., 2010; Hamadani et al., 2011), Nepal (Parajuli et al., 2014; Parajuli et al., 2015b; Parajuli et al., 2015a), the United States (Signes-Pastor et al., 2022; Nozadi et al., 2021), Spain (Soler-Blasco et al., 2022), Tanzania (Nyanza et al., 2021), and Canada (Patti et al., 2022) (see Figure 3-41).

Some cohort studies on the linkage between arsenic and developmental neurocognitive effects suggest that results may differ based on timing of exposure or outcome assessment. For example, three prospective cohort studies evaluated the association between arsenic and developmental neurocognition using a cohort of maternal-infant pairs in Nepal (Parajuli et al., 2014; Parajuli et al., 2015b; Parajuli et al., 2015a). These studies estimated *in utero* exposure using arsenic levels in cord blood (mean 1.33 µg/L) and assessed mental development index (MDI) from the Bayley Scale of Infant Development at 6 months (Parajuli et al., 2014), 24 months (Parajuli et al., 2015a), and 36 months of age (Parajuli et al., 2015b). No statistically significant association was found between arsenic exposure in cord blood at delivery and mental development at any time point (6, 24, or 36 months of age; n = 94, 74, and 70, respectively), though suggestive positive and inverse associations were observed (beta (95% CI); 6 months: 1.01 (−4.53, 6.55); 24 months: −10.15 (−25.54, 5.23); 36 months: 2.55 (−9.07, 14.17)) (Parajuli et al., 2014; Parajuli et al., 2015a; Parajuli et al., 2015b). Maternal arsenic methylation, which results in lower exposure of toxic metabolites to the fetus, increases with advancing gestation (Section 1.5.1), which may partially explain these null results for late pregnancy exposure.

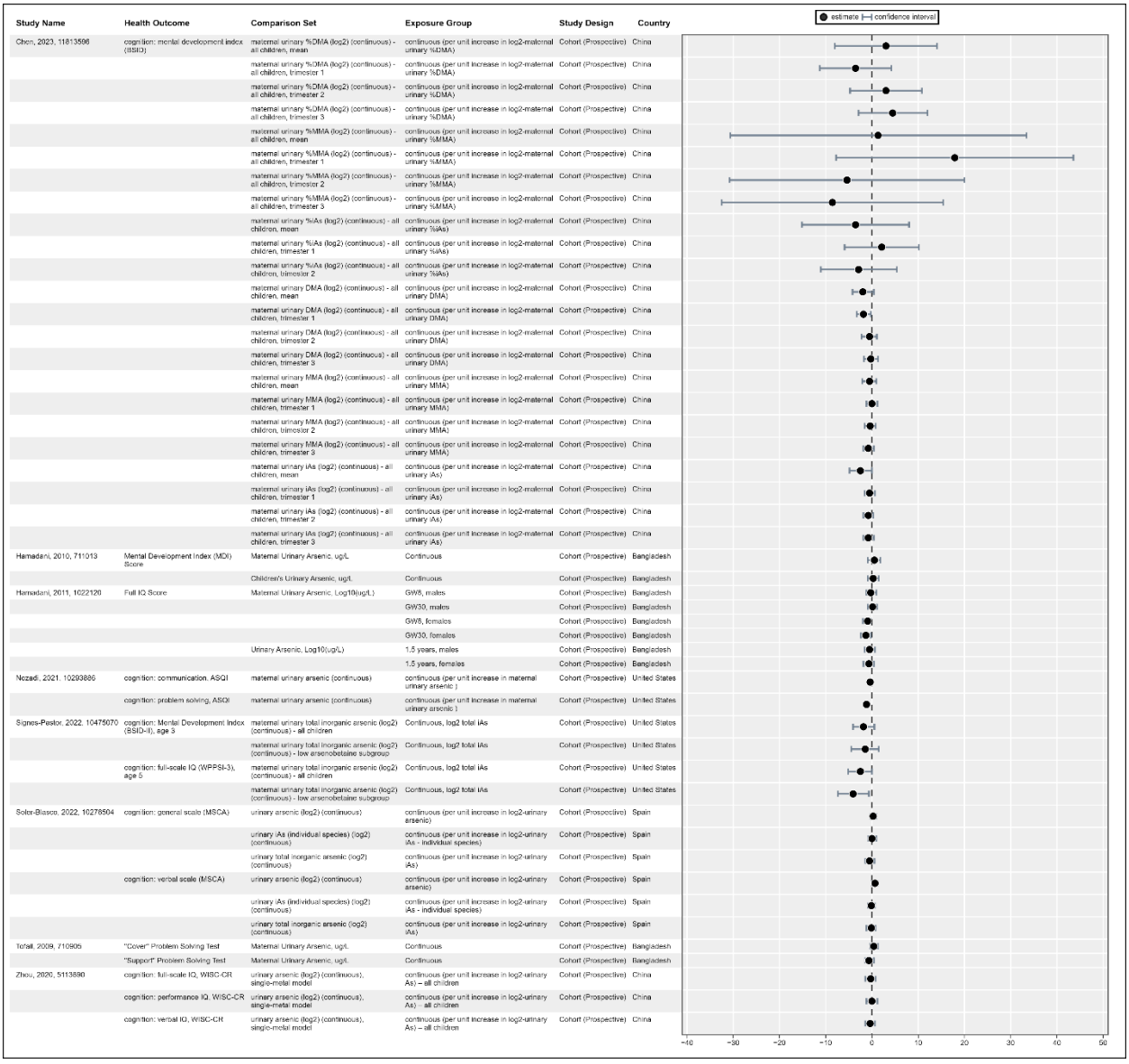
In Bangladesh, three studies evaluated high-level arsenic exposure and developmental neurocognition using a cohort of pregnant women enrolled in the Maternal and Infant Nutritional Intervention at Matlab (MINIMat) study (Hamadani et al., 2010; Hamadani et al., 2011; Tofail et al., 2009) (see Figure 3-41). Tofail et al. (2009) assessed problem solving in infants (mean age 7.4 months); the authors estimated *in utero* arsenic exposure using maternal urinary arsenic levels at gestational week (GW) 8 and 30 (median: 81 and 84 µg/L, respectively). These exposure windows capture both early and late pregnancy. The authors found no associations with problem solving. A follow-up study by Hamadani et al. (2010) assessed mental development in infants 18 months of age; the authors also evaluated language comprehension and expression. Consistent with Tofail et al. (2009), Hamadani et al. (2010) found no association between either maternal urinary (mean: 96.3 µg/L) or infant urinary arsenic levels (mean: 34.6 µg/L) and impaired neurodevelopment. For both of these studies, the authors posited that the impacts of exposure may become more apparent at later ages.

Hamadani et al. (2011) followed up with children from the same cohort at 5 years of age and assessed IQ with maternal urinary arsenic and urinary arsenic levels in children. A statistically significant inverse association between verbal IQ score and arsenic was found based on both maternal urinary arsenic at GW 8 (beta (95% CI): −0.9 (−1.7, −0.13) and child urinary arsenic at 1.5 years of age (beta (95% CI): −0.9 (−1.7, −0.10). Early gestation (i.e., GW 8) may be a particular window of vulnerability, given limited maternal arsenic methylation capacity (Section 1.5.1). When stratified by sex, the authors observed a statistically significant association between higher maternal urinary arsenic levels (GW 8 and GW 30) and child urinary arsenic levels (5 years of age) and decreased verbal IQ score in girls but not in boys. Similarly, in the stratified analysis, a significant association was found between decreased full-scale IQ score and maternal and child urinary arsenic levels at GW 30 and 5 years of age, respectively, in girls but not in boys (Hamadani et al., 2011).

Additional cohort studies utilizing a variety of exposure markers, including fingernail, urine, hair, and cord blood from diverse countries, including China, Taiwan, United States, Canada, Spain, and Bangladesh (Wang et al., 2022b; Vahter et al., 2020; Soler-Blasco et al., 2022; Signes-Pastor et al., 2022; Patti et al., 2022; Nozadi et al., 2021; Jiang et al., 2022; Chen et al., 2023) also suggest the potential importance of exposure timing. Maternal urinary arsenic in early pregnancy (median: 82 μg/L), but not late pregnancy, showed inverse associations with full developmental scores (quintiles 2–4: beta (95% CI): −4.52 (−8.61, −0.43); −5.91 (−10.0, −1.77); −5.98 (−10.2, −1.77), respectively, compared with quintile 1) and with verbal comprehension (quintiles 2–4: beta (95% CI): −1.90 (−3.24, −0.56); −1.50 (−2.86, −0.15); −1.89 (−3.27, −0.50), respectively, compared with quintile 1) in a cohort in Bangladesh (Vahter et al., 2020). These differing results based on different stages of pregnancy (early vs. late) may reflect changes in maternal arsenic metabolism over increasing gestation (see Section 1.5.1). In another cohort study looking at early pregnancy exposures, authors observed that urinary monomethylarsonic acid (MMA) concentrations measured in the first trimester of pregnancy (geometric mean: 0.34 μg/g) were inversely associated with the scores for the general, verbal, quantitative, memory, and working memory scales of children aged 4–5 years in Spain (beta (95% CI); general: −1.37 (−2.33, −0.41); verbal: −1.18 (−2.13, −0.23); quantitative: −1.23 (−2.20, −0.27); memory: −1.19 (−2.17, −0.20); working memory: −0.96 (−1.90, −0.02)) (Soler-Blasco et al., 2022). Similarly, in Canada, first trimester urinary DMA concentrations (median: 2.23 μg/L) were associated with decreased odds of optimal neurodevelopment at 3 years of age (based on both cognitive and behavioral components), though the confidence interval included the null (OR (95% CI): 0.44 (0.19, 1.02) (Patti et al., 2022). Effects were more mixed when evaluating periods of exposure that included later pregnancy or delivery. For example, maternal urinary arsenic measurements at 26 weeks pregnancy (median (IQR): 3.63 (2.40–5.86) μg/L) was associated with suggestive decreases (with confidence intervals including the null) in mental development index (MDI) as well as full-scale IQ (FSIQ) among a U.S. cohort (n = 260) of children at ages 2, 3,5, and 8 years old (beta (95% CI); MDI at 2 years: −1.1 (−3.5, 1.2);

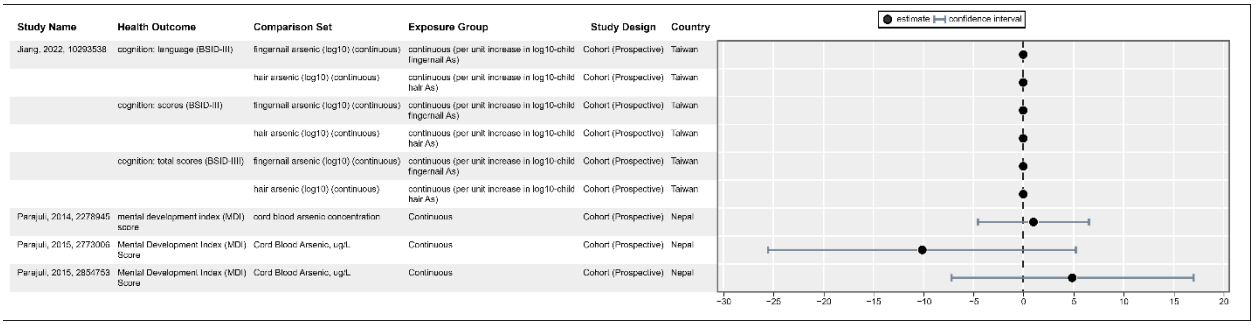
MDI at 3 years: −1.8 (−4.1, 0.5); FSIQ at 5 years: −2.5 (−5.1, 0.0); FSIQ at 8 years: −1.7 (−4.5, 1.1)) (Signes-Pastor et al., 2022).

In some cases, however, periods of exposure that included later pregnancy still demonstrated adverse effects with developmental neurocognitive effects. For example, in the Navajo Birth Cohort Study (n = 327), arsenic measured in maternal urine at the time of delivery (geometric mean: 6.13 µg/L) was inversely associated with problem-solving scores in infants at ages 10 to 13 months (beta (SD): −1.25 (0.48)) (Nozadi et al., 2021). Similarly, in a cohort from China (n = 148), authors examined intelligence in school-aged children (mean = 7.5 years). Using cord blood arsenic concentrations at delivery (median (IQR): 1.64 (0.76–2.93) µg/L), the authors observed suggestive inverse associations with children's verbal intelligence quotient, with stronger and statistically significant impacts in girls at lower exposures (Q2 vs. ref: −13.63 (−24.16, −3.09); Q3 vs. ref: −5.25 (−14.81, 4.32); Q4 vs. ref: −3.54 (−14.02, 6.94)) (Wang et al., 2022b). Another cohort study based in China observed that urinary iAs during pregnancy (GM averaged across three trimesters: 3.26 µg/L) was associated with decreased MDI scores in children at age 2 years (beta (95% CI): −2.45 (−4.86, −0.05)) (Chen et al., 2023). However, in a cohort based in Taiwan, there was no association between meconium arsenic concentrations and cognitive and language scores at age 3 (Jiang et al., 2022).



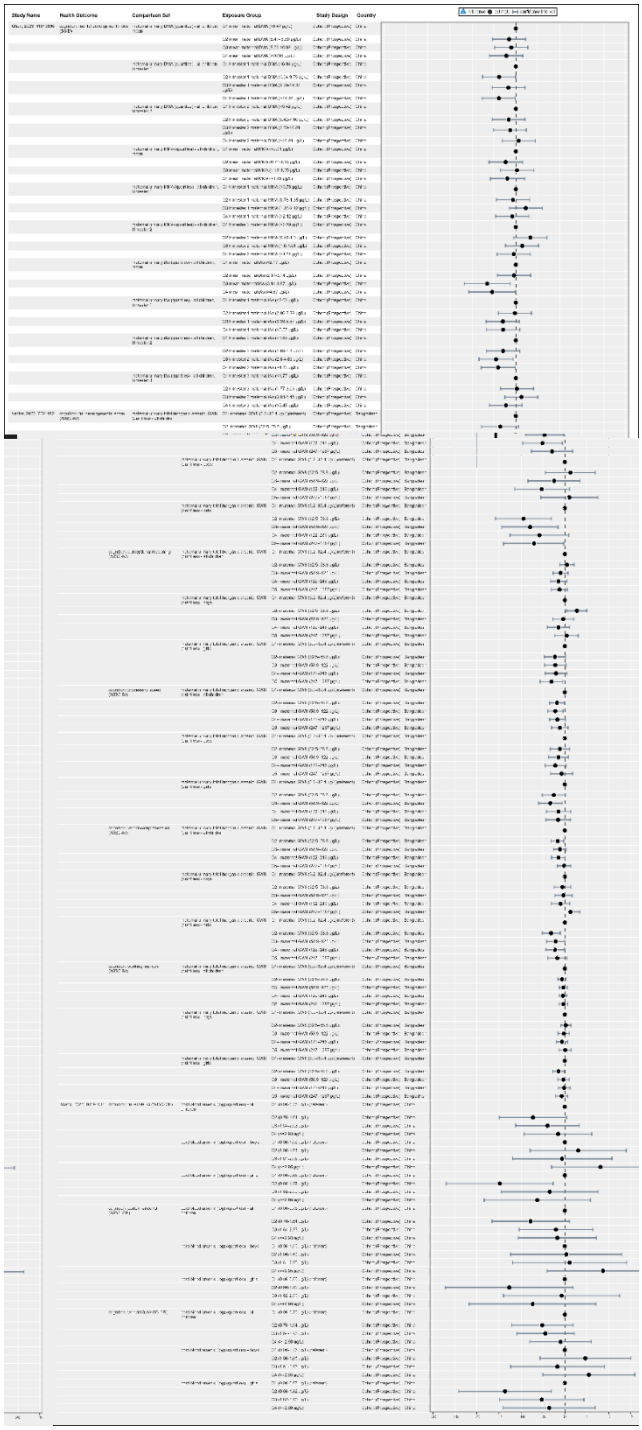
Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Chen, 2023, 11813596	cognition: mental development index (BSID)	maternal urinary %DMA (log2) (continuous) - all children, mean	continuous (per unit increase in log2-maternal urinary %DMA)	Cohort (Prospective)	China
		maternal urinary %DMA (log2) (continuous) - all children, trimester 1	continuous (per unit increase in log2-maternal urinary %DMA)	Cohort (Prospective)	China
		maternal urinary %DMA (log2) (continuous) - all children, trimester 2	continuous (per unit increase in log2-maternal urinary %DMA)	Cohort (Prospective)	China
		maternal urinary %DMA (log2) (continuous) - all children, trimester 3	continuous (per unit increase in log2-maternal urinary %DMA)	Cohort (Prospective)	China
		maternal urinary %MMA (log2) (continuous) - all children, mean	continuous (per unit increase in log2-maternal urinary %MMA)	Cohort (Prospective)	China
		maternal urinary %MMA (log2) (continuous) - all children, trimester 1	continuous (per unit increase in log2-maternal urinary %MMA)	Cohort (Prospective)	China
		maternal urinary %MMA (log2) (continuous) - all children, trimester 2	continuous (per unit increase in log2-maternal urinary %MMA)	Cohort (Prospective)	China
		maternal urinary %MMA (log2) (continuous) - all children, trimester 3	continuous (per unit increase in log2-maternal urinary %MMA)	Cohort (Prospective)	China
		maternal urinary %iAs (log2) (continuous) - all children, mean	continuous (per unit increase in log2-maternal urinary %iAs)	Cohort (Prospective)	China
		maternal urinary %iAs (log2) (continuous) - all children, trimester 1	continuous (per unit increase in log2-maternal urinary %iAs)	Cohort (Prospective)	China
		maternal urinary %iAs (log2) (continuous) - all children, trimester 2	continuous (per unit increase in log2-maternal urinary %iAs)	Cohort (Prospective)	China
		maternal urinary DMA (log2) (continuous) - all children, mean	continuous (per unit increase in log2-maternal urinary DMA)	Cohort (Prospective)	China
		maternal urinary DMA (log2) (continuous) - all children, trimester 1	continuous (per unit increase in log2-maternal urinary DMA)	Cohort (Prospective)	China
		maternal urinary DMA (log2) (continuous) - all children, trimester 2	continuous (per unit increase in log2-maternal urinary DMA)	Cohort (Prospective)	China
		maternal urinary DMA (log2) (continuous) - all children, trimester 3	continuous (per unit increase in log2-maternal urinary DMA)	Cohort (Prospective)	China
		maternal urinary MMA (log2) (continuous) - all children, mean	continuous (per unit increase in log2-maternal urinary MMA)	Cohort (Prospective)	China
		maternal urinary MMA (log2) (continuous) - all children, trimester 1	continuous (per unit increase in log2-maternal urinary MMA)	Cohort (Prospective)	China
		maternal urinary MMA (log2) (continuous) - all children, trimester 2	continuous (per unit increase in log2-maternal urinary MMA)	Cohort (Prospective)	China
		maternal urinary MMA (log2) (continuous) - all children, trimester 3	continuous (per unit increase in log2-maternal urinary MMA)	Cohort (Prospective)	China
		maternal urinary iAs (log2) (continuous) - all children, mean	continuous (per unit increase in log2-maternal urinary iAs)	Cohort (Prospective)	China
		maternal urinary iAs (log2) (continuous) - all children, trimester 1	continuous (per unit increase in log2-maternal urinary iAs)	Cohort (Prospective)	China
		maternal urinary iAs (log2) (continuous) - all children, trimester 2	continuous (per unit increase in log2-maternal urinary iAs)	Cohort (Prospective)	China
		maternal urinary iAs (log2) (continuous) - all children, trimester 3	continuous (per unit increase in log2-maternal urinary iAs)	Cohort (Prospective)	China
Hamadani, 2010, 711013	Mental Development Index (MDI) Score	Maternal Urinary Arsenic, ug/L	Continuous	Cohort (Prospective)	Bangladesh
		Children's Urinary Arsenic, ug/L	Continuous	Cohort (Prospective)	Bangladesh
Hamadani, 2011, 1022120	Full IQ Score	Maternal Urinary Arsenic, Log10(ug/L)	GW8, males	Cohort (Prospective)	Bangladesh
			GW30, males	Cohort (Prospective)	Bangladesh
			GW8, females	Cohort (Prospective)	Bangladesh
			GW30, females	Cohort (Prospective)	Bangladesh
		Urinary Arsenic, Log10(ug/L)	1.5 years, males	Cohort (Prospective)	Bangladesh
			1.5 years, females	Cohort (Prospective)	Bangladesh
Nozadi, 2021, 10293886	cognition: communication, ASQI	maternal urinary arsenic (continuous)	continuous (per unit increase in maternal urinary arsenic)	Cohort (Prospective)	United States
	cognition: problem solving, ASQI	maternal urinary arsenic (continuous)	continuous (per unit increase in maternal urinary arsenic)	Cohort (Prospective)	United States
Signes-Pastor, 2022, 10475070	cognition: Mental Development Index (BSID-II), age 3	maternal urinary total inorganic arsenic (log2) (continuous) - all children	Continuous, log2 total iAs	Cohort (Prospective)	United States
		maternal urinary total inorganic arsenic (log2) (continuous) - low arsenobetaine subgroup	Continuous, log2 total iAs	Cohort (Prospective)	United States
	cognition: full-scale IQ (WPPSI-3), age 5	maternal urinary total inorganic arsenic (log2) (continuous) - all children	Continuous, log2 total iAs	Cohort (Prospective)	United States
		maternal urinary total inorganic arsenic (log2) (continuous) - low arsenobetaine subgroup	Continuous, log2 total iAs	Cohort (Prospective)	United States
Soler-Blasco, 2022, 10278504	cognition: general scale (MSCA)	urinary arsenic (log2) (continuous)	continuous (per unit increase in log2-urinary arsenic)	Cohort (Prospective)	Spain
		urinary iAs (individual species) (log2) (continuous)	continuous (per unit increase in log2-urinary iAs - individual species)	Cohort (Prospective)	Spain
		urinary total inorganic arsenic (log2) (continuous)	continuous (per unit increase in log2-urinary iAs)	Cohort (Prospective)	Spain
	cognition: verbal scale (MSCA)	urinary arsenic (log2) (continuous)	continuous (per unit increase in log2-urinary arsenic)	Cohort (Prospective)	Spain
		urinary iAs (individual species) (log2) (continuous)	continuous (per unit increase in log2-urinary iAs - individual species)	Cohort (Prospective)	Spain
		urinary total inorganic arsenic (log2) (continuous)	continuous (per unit increase in log2-urinary iAs)	Cohort (Prospective)	Spain
Tofail, 2009, 710905	"Cover" Problem Solving Test	Maternal Urinary Arsenic, ug/L	Continuous	Cohort (Prospective)	Bangladesh
	"Support" Problem Solving Test	Maternal Urinary Arsenic, ug/L	Continuous	Cohort (Prospective)	Bangladesh
Zhou, 2020, 5113590	cognition: full-scale IQ, WISC-CR	urinary arsenic (log2) (continuous), single-metal model	continuous (per unit increase in log2-urinary As) – all children	Cohort (Prospective)	China
	cognition: performance IQ, WISC-CR	urinary arsenic (log2) (continuous), single-metal model	continuous (per unit increase in log2-urinary As) – all children	Cohort (Prospective)	China
	cognition: verbal IQ, WISC-CR	urinary arsenic (log2) (continuous), single-metal model	continuous (per unit increase in log2-urinary As) – all children	Cohort (Prospective)	China

(a) Difference measures, urine biomarkers, continuous exposures



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Jiang, 2022, 10293538	cognition: language (BSID-III)	fingernail arsenic (log10) (continuous)	continuous (per unit increase in log10-child fingernail As)	Cohort (Prospective)	Taiwan
		hair arsenic (log10) (continuous)	continuous (per unit increase in log10-child hair As)	Cohort (Prospective)	Taiwan
	cognition: scores (BSID-III)	fingernail arsenic (log10) (continuous)	continuous (per unit increase in log10-child fingernail As)	Cohort (Prospective)	Taiwan
		hair arsenic (log10) (continuous)	continuous (per unit increase in log10-child hair As)	Cohort (Prospective)	Taiwan
	cognition: total scores (BSID-III)	fingernail arsenic (log10) (continuous)	continuous (per unit increase in log10-child fingernail As)	Cohort (Prospective)	Taiwan
		hair arsenic (log10) (continuous)	continuous (per unit increase in log10-child hair As)	Cohort (Prospective)	Taiwan
Parajuli, 2014, 2278945	mental development index (MDI) score	cord blood arsenic concentration	Continuous	Cohort (Prospective)	Nepal
Parajuli, 2015, 2773006	Mental Development Index (MDI) Score	Cord Blood Arsenic, ug/L	Continuous	Cohort (Prospective)	Nepal
Parajuli, 2015, 2854753	Mental Development Index (MDI) Score	Cord Blood Arsenic, ug/L	Continuous	Cohort (Prospective)	Nepal

(b) Difference measures, nonurine biomarkers, continuous exposures



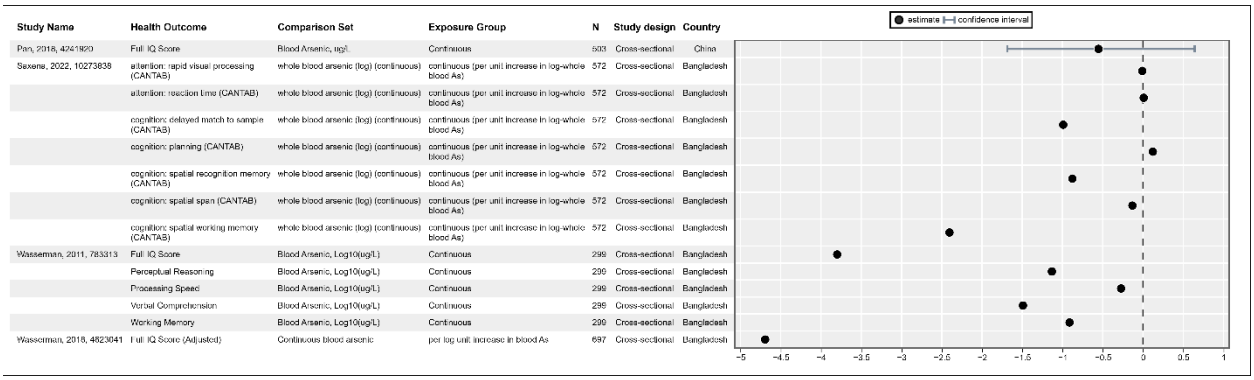
(c) Difference measures, biomarkers, categorical exposures

Figure 3-41. Thumbnail schematic of cohort and case-control studies addressing the association between inorganic arsenic exposure and developmental neurocognitive effects (a) difference measures, urine biomarkers, continuous exposure; (b) difference measures, non-urine biomarkers, continuous exposure; (c) difference measures, biomarkers, categorical exposure (see interactive data graphic).

Cross-sectional & ecological studies

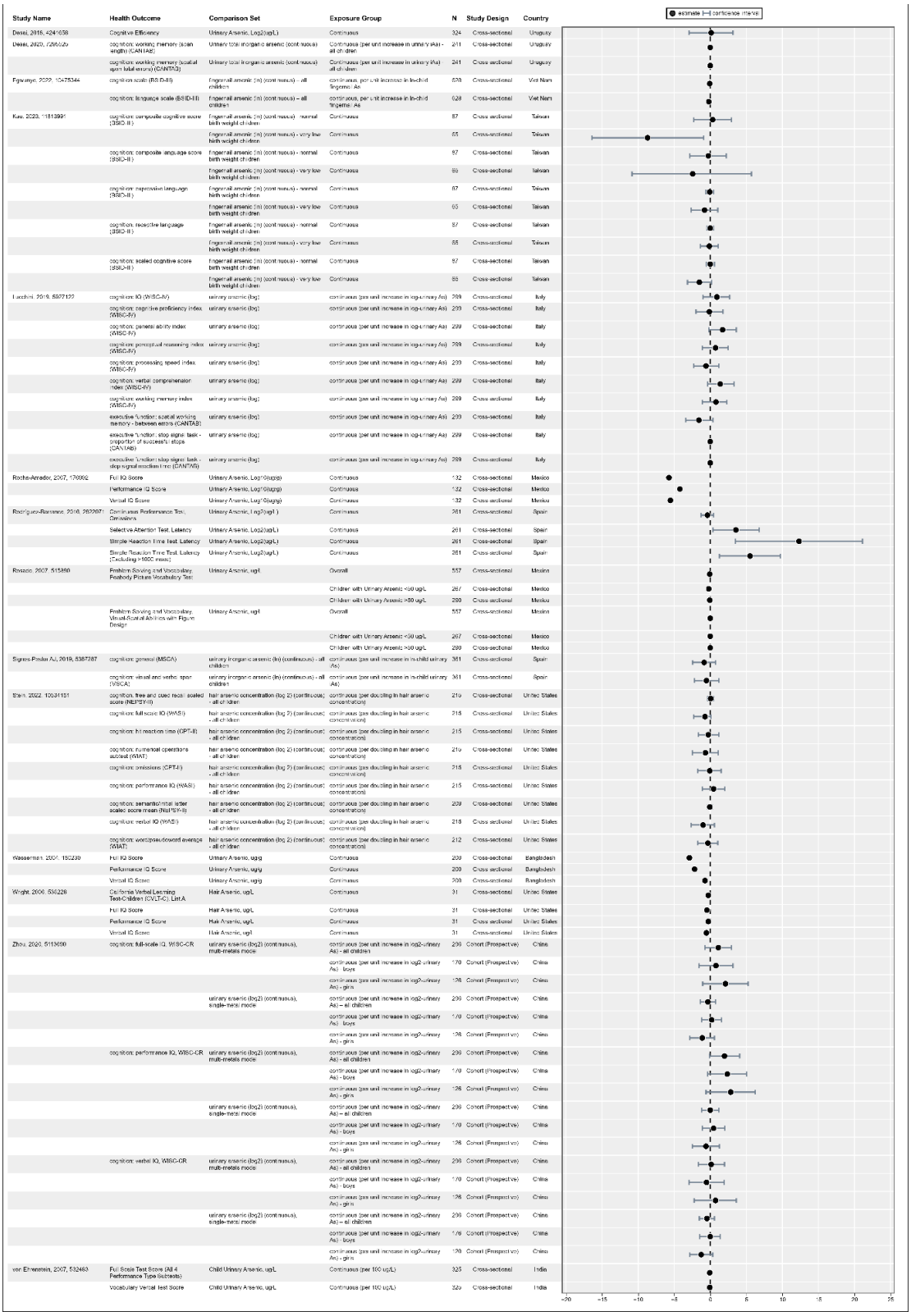
Additional evidence for an association between arsenic exposure and developmental neurocognitive deficits comes from 27 cross-sectional studies conducted in the United States (Wright et al., 2006; Wasserman et al., 2014; Stein et al., 2022); Mexico (Rosado et al., 2007; Rocha-Amador et al., 2007; Calderón et al., 2001); Bangladesh (Wasserman et al., 2004; Wasserman et al., 2007; Wasserman et al., 2011; Wasserman et al., 2018; Saxena et al., 2022; Nahar et al., 2014b; Nahar et al., 2014a); China (Zhou et al., 2020; Wang et al., 2006; Pan et al., 2018); Taiwan (Kao et al., 2023a); India (von Ehrenstein et al., 2007; Vaidya et al., 2023); Cambodia (Vibol et al., 2015); Vietnam (Egwunye et al., 2022); Uruguay (Desai et al., 2018; Desai et al., 2020b; Desai et al., 2020a); Italy (Lucchini et al., 2019); and Spain (Rodríguez-Barranco et al., 2016; Signes-Pastor et al., 2019b) (see Figure 3-42). The majority of the cross-sectional studies evaluated populations that had experienced chronic or lifelong exposure to arsenic, reducing concern about temporality normally present for this study design. There was also one ecological study based in Australia (Dong et al., 2015) as well as one cross-sectional analysis from a cohort study (Vahter et al., 2020).

In several studies from the United States, the relationship between arsenic exposure and intellectual function was examined among school-aged children (see Figure 3-42). Wasserman et al. (2014) used arsenic levels in drinking water and toenails (mean 9.88 μg/L and 4.65 μg/g, respectively) to estimate arsenic exposure with intellectual quotient (IQ) and cognitive performance. Compared with children exposed to <5 μg/L arsenic in drinking water, those exposed to arsenic levels 5–10 μg/L had statistically significantly lower FSIQ scores and lower scores in perceptual reasoning, working memory, and verbal comprehension (beta (SE); FSIQ: −6.09 (1.98); perceptual reasoning: −4.97 (2.14); working memory: −4.88 (2.24); verbal comprehension: −6.22 (2.49). No association was observed between these measures of intellectual function and toenail arsenic concentrations (Wasserman et al., 2014). Wright et al. (2006) measured arsenic levels in hair (mean 17.8 ppb) of children (11–13 years old) in the U.S. and assessed IQ, complex nonverbal cognitive abilities, verbal learning and memory, and learning and memory. The authors reported a statistically significant inverse association between hair arsenic levels and verbal IQ and FSIQ (beta (SE); verbal IQ: −0.51 (0.16); FSIQ: −0.44 (0.17)) (see Figure 3-42). Stein et al. (2022) also observed inverse associations between hair arsenic (median: 0.018 μg/g) and both full-scale IQ and verbal IQ, though confidence intervals included the null (beta (95% CI); full-scale IQ: −0.73 (−2.32, 0.86); verbal IQ: −1.02 (−2.63, 0.59)).



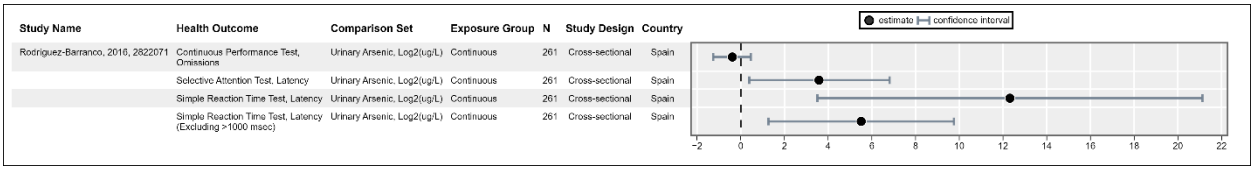
Study Name	Health Outcome	Comparison Set	Exposure Group	N	Study design	Country
Pan, 2018, 4241920	Full IQ Score	Blood Arsenic, ug/l	Continuous	503	Cross-sectional	China
Saxena, 2022, 10273838	attention: rapid visual processing (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
	attention: reaction time (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
	cognition: delayed match to sample (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
	cognition: planning (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
	cognition: spatial recognition memory (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
	cognition: spatial span (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
	cognition: spatial working memory (CANTAB)	whole blood arsenic (log) (continuous)	continuous (per unit increase in log-whole blood As)	572	Cross-sectional	Bangladesh
Wasserman, 2011, 783313	Full IQ Score	Blood Arsenic, Log10(ug/L)	Continuous	299	Cross-sectional	Bangladesh
	Perceptual Reasoning	Blood Arsenic, Log10(ug/L)	Continuous	299	Cross-sectional	Bangladesh
	Processing Speed	Blood Arsenic, Log10(ug/L)	Continuous	299	Cross-sectional	Bangladesh
	Verbal Comprehension	Blood Arsenic, Log10(ug/L)	Continuous	299	Cross-sectional	Bangladesh
	Working Memory	Blood Arsenic, Log10(ug/L)	Continuous	299	Cross-sectional	Bangladesh
Wasserman, 2018, 4823041	Full IQ Score (Adjusted)	Continuous blood arsenic	per log unit increase in blood As	697	Cross-sectional	Bangladesh

(a) Difference measures, blood biomarkers, continuous exposures



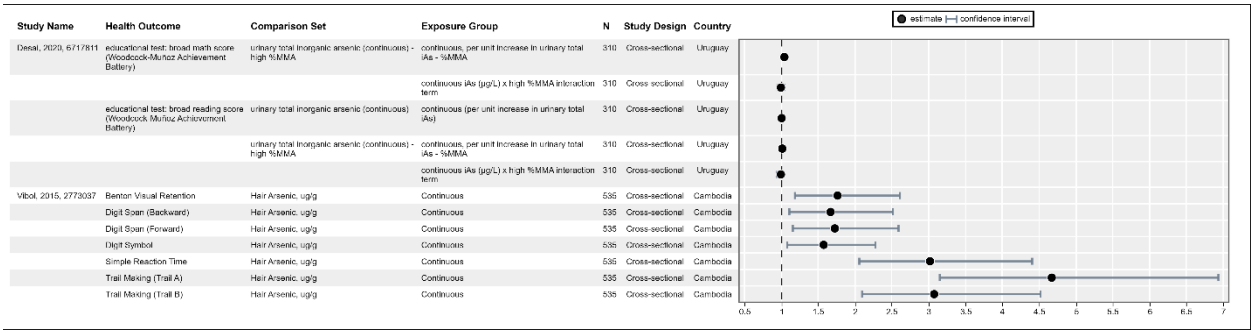
Study Name	Health Outcome	Comparison Set	Exposure Group	N	Study Design	Country
Dassi, 2015, 4241658	Cognitive Efficiency	Urinary Arsenic, Log2(ug/L)	Continuous	324	Cross-sectional	Uruguay
Dassi, 2020, 7256626	cognition: working memory (span length) (CANTAB)	Urinary total inorganic arsenic (cont.tuous)	Continuous (per unit increase in urinary iAs) - all children	241	Cross-sectional	Uruguay
	cognition: working memory (spatial span total errors) (CANTAB)	Urinary total inorganic arsenic (cont.tuous)	Continuous (per unit increase in urinary iAs) - all children	241	Cross-sectional	Uruguay
Figueroa, 2022, 10475344	cognition scale (RSID-III)	Fingernail arsenic (in) (cont.tuous) – all children	continuous, per unit increase in ln-child fingernail As	628	Cross-sectional	Viet Nam
	cognition: language scale (BSID-III)	Fingernail arsenic (in) (cont.tuous) – all children	continuous, per unit increase in ln-child fingernail As	628	Cross-sectional	Viet Nam
Kau, 2023, 11813991	cognition: composite cognitive score (3SID-III)	Fingernail arsenic (in) (cont.tuous) - normal birth weight children	Continuous	87	Cross-sectional	Taiwan
		Fingernail arsenic (in) (cont.tuous) - very low birth weight children	Continuous	65	Cross-sectional	Taiwan
	cognition: composite language score (3SID-III)	Fingernail arsenic (in) (cont.tuous) - normal birth weight children	Continuous	87	Cross-sectional	Taiwan
		Fingernail arsenic (in) (cont.tuous) - very low birth weight children	Continuous	65	Cross-sectional	Taiwan
	cognition: expressive language (3SID-III)	Fingernail arsenic (in) (cont.tuous) - normal birth weight children	Continuous	87	Cross-sectional	Taiwan
		Fingernail arsenic (in) (cont.tuous) - very low birth weight children	Continuous	65	Cross-sectional	Taiwan
	cognition: receptive language (3SID-III)	Fingernail arsenic (in) (cont.tuous) - normal birth weight children	Continuous	87	Cross-sectional	Taiwan
		Fingernail arsenic (in) (cont.tuous) - very low birth weight children	Continuous	65	Cross-sectional	Taiwan
	cognition: scaled cognitive score (3SID-III)	Fingernail arsenic (in) (cont.tuous) - normal birth weight children	Continuous	87	Cross-sectional	Taiwan
		Fingernail arsenic (in) (cont.tuous) - very low birth weight children	Continuous	65	Cross-sectional	Taiwan
Lucchini, 2019, 5807122	cognition: IQ (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	cognition: cognitive proficiency index (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	cognition: general ability index (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	cognition: perceptual reasoning index (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	cognition: processing speed index (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	cognition: verbal comprehension index (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	cognition: working memory index (WISC-IV)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	executive function: scatcat working memory - between errors (CANTAB)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	executive function: stop signal task - proportion of success ful stops (CANTAB)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
	executive function: stop signal task - stop signal reaction time (CANTAB)	urinary arsenic (log)	continuous (per unit increase in log-urinary As)	299	Cross-sectional	Italy
Rocha-Amador, 2007, 176662	Full IQ Score	Urinary Arsenic, Log10(ug/g)	Continuous	132	Cross-sectional	Mexico
	Performance IQ Score	Urinary Arsenic, Log10(ug/g)	Continuous	132	Cross-sectional	Mexico
	Verbal IQ Score	Urinary Arsenic, Log10(ug/g)	Continuous	132	Cross-sectional	Mexico
Rodriguez-Barranco, 2013, 2823967	Continuous Performance Test, Omissions	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
	Selective Attention Test, Latency	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
	Simple Reaction Time Test, Latency	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
	Simple Reaction Time Test, Latency (Excluding >1000 msec)	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
Rosado, 2007, 515886	Problem Solving and Vocabulary, Peabody Picture Vocabulary Test	Urinary Arsenic, ug/l	Overall	557	Cross-sectional	Mexico
			Children with Urinary Arsenic <50 ug/L	267	Cross-sectional	Mexico
			Children with Urinary Arsenic >50 ug/L	290	Cross-sectional	Mexico
	Problem Solving and Vocabulary, Visual-Scatcat Abilities with Figure Design	Urinary Arsenic, ug/l	Overall	557	Cross-sectional	Mexico
			Children with Urinary Arsenic <50 ug/L	267	Cross-sectional	Mexico
			Children with Urinary Arsenic >50 ug/L	290	Cross-sectional	Mexico
Signes-Pastor AJ, 2019, 6367287	cognition: general (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-child urinary As)	361	Cross-sectional	Spain
	cognition: visual and verbal span (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	continuous (per unit increase in ln-child urinary As)	361	Cross-sectional	Spain
Stein, 2022, 10934151	cognition: free and cued recall: scaled score (NEPSY-II)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	210	Cross-sectional	United States
	cognition: full scale IQ (WASI)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	215	Cross-sectional	United States
	cognition: hit reaction time (CPT-II)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	215	Cross-sectional	United States
	cognition: numerical operations subtest (WIAT)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	210	Cross-sectional	United States
	cognition: omissions (CPT-II)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	215	Cross-sectional	United States
	cognition: performance IQ (WASI)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	215	Cross-sectional	United States
	cognition: semantic/initial letter scaled score mean (NEPSY-II)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	209	Cross-sectional	United States
	cognition: verbal IQ (WASI)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	215	Cross-sectional	United States
	cognition: word/pseudoword average (WIAT)	hair arsenic concentration (log 2) (continuous) - all children	continuous (per doubling in hair arsenic concentration)	212	Cross-sectional	United States
Wasserman, 2004, 180230	Full IQ Score	Urinary Arsenic, ug/g	Continuous	200	Cross-sectional	Bangladesh
	Performance IQ Score	Urinary Arsenic, ug/g	Continuous	200	Cross-sectional	Bangladesh
	Verbal IQ Score	Urinary Arsenic, ug/g	Continuous	200	Cross-sectional	Bangladesh
Wright, 2006, 536228	California Verbal Learning Test-Children (CVLT-C): List A	Hair Arsenic, ug/L	Continuous	31	Cross-sectional	United States
	Full IQ Score	Hair Arsenic, ug/L	Continuous	31	Cross-sectional	United States
	Performance IQ Score	Hair Arsenic, ug/L	Continuous	31	Cross-sectional	United States
	Verbal IQ Score	Hair Arsenic, ug/l	Continuous	31	Cross-sectional	United States
Zhou, 2020, 5113699	cognition: full-scale IQ, WISC-CR	urinary arsenic (log2) (continuous), multi-metals mode	continuous (per unit increase in log2-urinary As) - all children	290	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - boys	170	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - girls	126	Cohort (Prospective)	China
		urinary arsenic (log2) (continuous), single-metal mode	continuous (per unit increase in log2-urinary As) – all children	290	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - boys	170	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - girls	126	Cohort (Prospective)	China
	cognition: performance IQ, WISC-CR	urinary arsenic (log2) (continuous), multi-metals mode	continuous (per unit increase in log2-urinary As) - all children	290	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - boys	170	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - girls	126	Cohort (Prospective)	China
		urinary arsenic (log2) (continuous), single-metal mode	continuous (per unit increase in log2-urinary As) – all children	290	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - boys	170	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - girls	126	Cohort (Prospective)	China
	cognition: verbal IQ, WISC-CR	urinary arsenic (log2) (continuous), multi-metals mode	continuous (per unit increase in log2-urinary As) - all children	290	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - boys	170	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - girls	126	Cohort (Prospective)	China
		urinary arsenic (log2) (continuous), single-metal mode	continuous (per unit increase in log2-urinary As) – all children	290	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - boys	170	Cohort (Prospective)	China
			continuous (per unit increase in log2-urinary As) - girls	126	Cohort (Prospective)	China
von Ehrenstein, 2007, 532463	Full Scale Test Score (All 4 Performance Type Subtests)	Child Urinary Arsenic, ug/L	Continuous (per 100 ug/L)	325	Cross-sectional	India
	Vocabulary Verbal Test Score	Child Urinary Arsenic, ug/L	Continuous (per 100 ug/L)	329	Cross-sectional	India

(b) Difference measures, non-blood biomarkers, continuous exposures



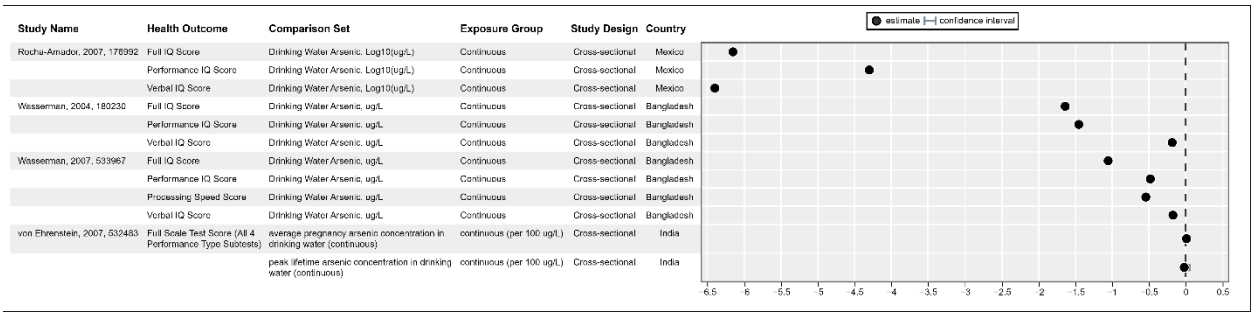
Study Name	Health Outcome	Comparison Set	Exposure Group	N	Study Design	Country
Rodriguez-Barranco, 2016, 2822071	Continuous Performance Test, Omissions	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
	Selective Attention Test, Latency	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
	Simple Reaction Time Test, Latency	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain
	Simple Reaction Time Test, Latency (Excluding >1000 msec)	Urinary Arsenic, Log2(ug/L)	Continuous	261	Cross-sectional	Spain

(c) Difference measures (latency & omission tests), non-blood biomarkers, continuous exposures



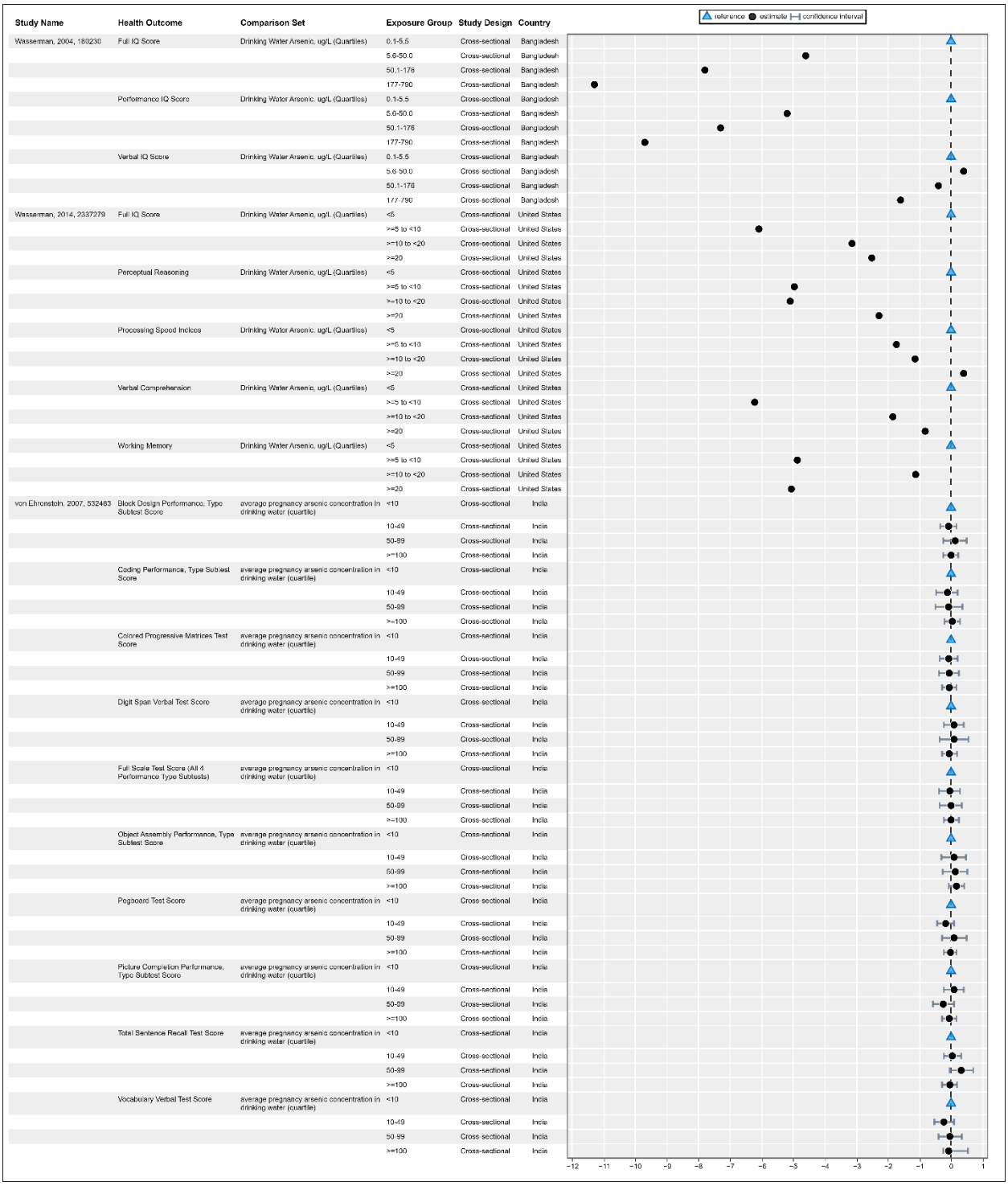
Study Name	Health Outcome	Comparison Set	Exposure Group	N	Study Design	Country
Desai, 2020, 6717811	educational test: broad math score (Woodcock-Muñoz Achievement Battery)	urinary total inorganic arsenic (continuous) - high %MMA	continuous, per unit increase in urinary total iAs - %MMA	310	Cross-sectional	Uruguay
			continuous iAs (µg/L) x high %MMA interaction term	310	Cross sectional	Uruguay
	educational test: broad reading score (Woodcock Muñoz Achievement Battery)	urinary total inorganic arsenic (continuous)	continuous (per unit increase in urinary total iAs)	310	Cross-sectional	Uruguay
		urinary total inorganic arsenic (continuous) - high %MMA	continuous, per unit increase in urinary total iAs - %MMA	310	Cross-sectional	Uruguay
			continuous iAs (µg/L) x high %MMA interaction term	310	Cross-sectional	Uruguay
Vibol, 2015, 2773037	Benton Visual Retention	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia
	Digit Span (Backward)	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia
	Digit Span (Forward)	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia
	Digit Symbol	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia
	Simple Reaction Time	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia
	Trail Making (Trail A)	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia
	Trail Making (Trail B)	Hair Arsenic, ug/g	Continuous	535	Cross-sectional	Cambodia

(d) Ratio measures (for impaired scores), biomarkers, continuous exposures



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Rocha-Amador, 2007, 176992	Full IQ Score	Drinking Water Arsenic, Log10(ug/L)	Continuous	Cross-sectional	Mexico
	Performance IQ Score	Drinking Water Arsenic, Log10(ug/L)	Continuous	Cross-sectional	Mexico
	Verbal IQ Score	Drinking Water Arsenic, Log10(ug/L)	Continuous	Cross-sectional	Mexico
Wasserman, 2004, 180230	Full IQ Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
	Performance IQ Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
	Verbal IQ Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
Wasserman, 2007, 533967	Full IQ Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
	Performance IQ Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
	Processing Speed Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
	Verbal IQ Score	Drinking Water Arsenic, ug/L	Continuous	Cross-sectional	Bangladesh
von Ehrenstein, 2007, 532483	Full Scale Test Score (All 4 Performance Type Subtests)	average pregnancy arsenic concentration in drinking water (continuous)	continuous (per 100 ug/L)	Cross-sectional	India
		peak lifetime arsenic concentration in drinking water (continuous)	continuous (per 100 ug/L)	Cross-sectional	India

(e) Difference measures, drinking water, continuous exposures



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Wasserman, 2004, 180230	Full IQ Score	Drinking Water Arsenic, ug/L (Quartiles)	0.1-5.5	Cross-sectional	Bangladesh
			5.6-50.0	Cross-sectional	Bangladesh
			50.1-176	Cross-sectional	Bangladesh
			177-790	Cross-sectional	Bangladesh
	Performance IQ Score	Drinking Water Arsenic, ug/L (Quartiles)	0.1-5.5	Cross-sectional	Bangladesh
			5.6-50.0	Cross-sectional	Bangladesh
			50.1-176	Cross-sectional	Bangladesh
			177-790	Cross-sectional	Bangladesh
	Verbal IQ Score	Drinking Water Arsenic, ug/L (Quartiles)	0.1-5.5	Cross-sectional	Bangladesh
			5.6-50.0	Cross-sectional	Bangladesh
			50.1-176	Cross-sectional	Bangladesh
			177-790	Cross-sectional	Bangladesh
Wasserman, 2014, 2337279	Full IQ Score	Drinking Water Arsenic, ug/L (Quartiles)	<5	Cross-sectional	United States
			>=5 to <10	Cross-sectional	United States
			>=10 to <20	Cross-sectional	United States
			>=20	Cross-sectional	United States
	Perceptual Reasoning	Drinking Water Arsenic, ug/L (Quartiles)	<5	Cross-sectional	United States
			>=5 to <10	Cross-sectional	United States
			>=10 to <20	Cross-sectional	United States
			>=20	Cross-sectional	United States
	Processing Speed Indices	Drinking Water Arsenic, ug/L (Quartiles)	<5	Cross-sectional	United States
			>=5 to <10	Cross-sectional	United States
			>=10 to <20	Cross-sectional	United States
			>=20	Cross-sectional	United States
	Verbal Comprehension	Drinking Water Arsenic, ug/L (Quartiles)	<5	Cross-sectional	United States
			>=5 to <10	Cross-sectional	United States
			>=10 to <20	Cross-sectional	United States
			>=20	Cross-sectional	United States
	Working Memory	Drinking Water Arsenic, ug/L (Quartiles)	<5	Cross-sectional	United States
			>=5 to <10	Cross-sectional	United States
			>=10 to <20	Cross-sectional	United States
			>=20	Cross-sectional	United States
von Ehrenstein, 2007, 532483	Block Design Performance, Type Subtest Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Coding Performance, Type Subtest Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Colored Progressive Matrices Test Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Digit Span Verbal Test Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Full Scale Test Score (All 4 Performance Type Subtests)	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Object Assembly Performance, Type Subtest Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Pegboard Test Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Picture Completion Performance, Type Subtest Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Total Sentence Recall Test Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India
	Vocabulary Verbal Test Score	average pregnancy arsenic concentration in drinking water (quartile)	<10	Cross-sectional	India
			10-49	Cross-sectional	India
			50-99	Cross-sectional	India
			>=100	Cross-sectional	India

(f) Difference measures, drinking water, categorical exposures

Figure 3-42. Thumbnail schematic of cross-sectional studies addressing the association between iAs exposure and developmental neurocognitive effects (a) difference measures, blood biomarkers, continuous exposures; (b) difference measures, non-blood biomarkers, continuous exposures; (c)

difference measures (latency & omission tests), non-blood biomarkers, continuous exposures; (d) ratio measures (for impaired scores), biomarkers, continuous exposures: (e) difference measures, drinking water, continuous exposures; (f) difference measures, drinking water, categorical exposures (see interactive data graphic).

In Mexico, students (6–8 years of age) living near a metallurgical smelter complex had cognitive effects measured, along with urinary arsenic (Rosado et al., 2007). The authors reported a significant inverse association between urinary arsenic levels (mean = 58.1 μg/L) and problem solving and vocabulary, memory, and attention scores. A statistically significant association was seen between urinary arsenic levels ≤50 μg/L and deficits in problem solving, vocabulary, and memory scores. Among children with urinary arsenic levels >50 μg/L, a statistically significant association was observed between urinary arsenic and deficits in problem solving, vocabulary, and attention scores. Also in Mexico, Rocha-Amador et al. (2007) studied children (6–10 years of age) in three rural areas where mean arsenic levels in drinking water ranged from 5.8 to 194 μg/L. The authors observed a statistically significant inverse association between urinary arsenic and full IQ scores (beta: −5.72) and nonsignificant associations with performance (beta: −4.19) and verbal IQ scores (beta: −5.50). All three outcomes were statistically significant in relation to drinking water (performance IQ: −4.30; verbal IQ: −6.40; full IQ: −6.15) (Rocha-Amador et al., 2007). Calderón et al. (2001) studied children (mean age = 7.5 years) in two Mexican communities (Martinez and Morales: mean urinary arsenic concentration 40.3 μg/g and 62.9 μg/g creatinine, respectively). While at the community level, the authors reported significantly lower full-scale ($p = 0.023$) and verbal IQ scores ($p = 0.038$) in Martinez (lower arsenic exposure) compared with Morales (higher arsenic exposure), they reported inverse correlations between urinary arsenic and several measures of intelligence among children in Morales (higher arsenic exposure) and between urinary arsenic and verbal IQ for both populations overall (Calderón et al., 2001).

Several cross-sectional studies identified in the literature review were conducted in India (von Ehrenstein et al., 2007; Vaidya et al., 2023) and Bangladesh (Nahar et al., 2014b; Nahar et al., 2014a; Wasserman et al., 2004; Wasserman et al., 2007; Wasserman et al., 2011; Saxena et al., 2022). For example, von Ehrenstein et al. (2007) used validated tests to assess neurodevelopmental effects in children 5–15 years of age in India. The authors reported a statistically significant inverse association between child urinary arsenic levels (mean = 78 μg/L) and performance on vocabulary and picture completion tests (>82.6 μg/L vs. ref; vocabulary: −0.28 (−0.55, −0.008); picture completion: −0.26 (−0.51, −0.01)). Also in India, urinary arsenic at ages 6–23 years was inversely associated with several measures of concurrent executive function (beta (95% CI); attention: −0.05 (−0.09, −0.01); working memory: −0.05 (−0.08, −0.01); set-shifting: −0.03 (−0.07, −0.004)) (Vaidya et al., 2023). In Bangladesh, Nahar et al. (2014a) assessed IQ in children grouped by urinary arsenic level (aged 4–5 years (mean = 126 μg/L); 9–10 years (mean = 181.9 μg/L)). Among the 4- to 5-year-old children, there was a statistically significant difference in IQ by exposure group (low = 137 μg/L; medium: 137 < 400 μg/L; and high: >400 μg/L). Among the 9- to 10-year-old

children, there was a statistically significant difference between IQ for the low versus medium exposure groups. Nahar et al. (2014b) used the same tests as Nahar et al. (2014a) to identify differences in IQ by arsenic exposure (mean drinking water arsenic levels = 71.7 μg/L; mean urinary arsenic levels = 205.3 μg/L) in adolescents (14–15 years of age) in Bangladesh. They identified lower IQ in groups with elevated arsenic (drinking water > 10 μg/L; urinary arsenic > 137 μg/L). In another study based in Bangladesh (Vahter et al., 2020), compared with the first urinary arsenic quintile at 10 years (<30 μg/L), children in the third and fourth quintiles (30–45 and 46–73 μg/L, respectively) had lower full developmental scores (beta (95% CI); third quartile: −7.23 (−11.3, −3.18); fourth quartile: −6.37 (−10.5, −2.22)). Analyses using children's hair arsenic concentrations showed similar results (Vahter et al., 2020). Additionally, Saxena et al. (2022) examined adolescents in Bangladesh and observed a statistically significant inverse association between blood arsenic and spatial working memory (beta (SE): −2.40 (1.10)).

There were several other studies based in Bangladesh from the same author group. Wasserman et al. (2004) found a statistically significant inverse association between high arsenic levels in drinking water (mean = 117.8 μg/L) and both full-scale and performance IQ scores in children aged 10 years (beta; full-scale: −1.64; performance: −1.45). In a later study looking at children 6 years of age, Wasserman et al. (2007) reported a statistically significant inverse association between similarly high arsenic levels in drinking water (mean = 120.1 μg/L) and full-scale IQ, performance IQ, and processing speed (beta (SE); full-scale: −1.06 (0.57); performance: −0.48 (0.24); processing speed: −0.54 (0.28)). Wasserman et al. (2011) found a statistically significant inverse association between blood arsenic levels (mean = 4.81 μg/L) and verbal comprehension in 8–11-year-olds (beta (SE): −1.49 (0.71)); the association with full-scale IQ was borderline significant (beta (SE): −3.80 (2.20)). In adolescents aged 14–16 years in Bangladesh, Wasserman et al. (2018) reported blood arsenic (mean: 4.84 μg/L) and creatinine-adjusted urinary arsenic (mean: 158 μg/g creatinine) levels were significantly negatively associated with various metrics of child intelligence, including verbal comprehension, processing speed, working memory, and perceptual reasoning (urinary arsenic only). For example, a doubling of blood arsenic was associated with a mean IQ score decrement of 3.3 points (95% CI: 1.1, 5.5) while a doubling of creatinine-adjusted urinary arsenic was associated with a mean decrement of 3.0 points (95% CI: 1.2, 4.5) (see Figure 3-42).

Other cross-sectional studies identified in the literature review included those conducted in China, Vietnam, Cambodia, Taiwan, Spain, and Uruguay. In 36-month-old children (n = 658) in Vietnam, authors reported that fingernail arsenic concentrations (median (IQR): 0.4 (0.3–0.5) μg/g) were significantly associated with reduced language scores (beta (95% CI): −0.19 (−0.32, −0.05)) (Egwunye et al., 2022). In north-central China, Wang et al. (2006) studied children aged 8–12 years and examined the association between IQ score and arsenic levels in drinking water in a rural community. The authors reported statistically significant differences between mean arsenic levels in drinking water and IQ score in both the high (190 μg/L) and medium (142 μg/L) arsenic groups

compared with the control group (2 μg/L). The IQ scores were 10 and 4 points lower, respectively, in the high and medium arsenic exposure groups compared with students in the control group. However, Pan et al. (2018) studied children aged 9–11 years to examine the association between IQ score and arsenic concentrations in blood and urine in southern China and observed no significant associations. Similarly, Zhou et al. (2020) observed no associations between arsenic concentration from children's urine samples at age 7–8 years (median (IQR): 26.05 (12.88–43.80) μg/L) and concurrent IQ. And among normal-birth-weight children at 2 years of age in Taiwan, fingernail arsenic (central tendency not reported) was not associated with cognitive scores (Kao et al., 2023a).

In Spain, Rodríguez-Barranco et al. (2016) assessed the association between urinary arsenic (geometric mean = 0.7 μg/L) and neurodevelopmental effects in children aged 6–9 years, finding statistically significant associations between higher concentrations of arsenic and impaired reaction time, including increased latency in the selective attention and simple reaction time tests (beta (95% CI); selective attention: 3.58 (0.37, 6.79); simple reaction time: 12.31 (3.51, 21.22)). Another study from Spain examining neuropsychological development observed suggestive inverse associations with the scores in the quantitative index and working memory function only in boys, using a spot urine sample (median: 4.85 μg/L) at ages 4–5 years (beta (95% CI); quantitative index: −2.69 (−5.36, 0.17); working memory: −2.56 (−5.36, 0.24)) (Signes-Pastor et al., 2019b).

In Uruguay, Desai et al. (2018) assessed the association between urinary arsenic levels (median: 11.6 μg/L) and cognitive performance in 5–8 year old children; no statistically significant associations between arsenic and cognitive abilities were seen. Similarly, Desai et al. (2020a) found no significant associations between urinary arsenic (median: 11.7 μg/L) and academic achievement measures. However, Desai et al. (2020b) found that urinary arsenic (median: 9.9 μg/L) was inversely associated with visual attention measures, including the number of stages completed in the visual attention task (beta (95% CI): −0.02 (−0.03, −0.002), pre-executive shift errors in the visual attention task (beta (95% CI): −0.08 (−0.14, −0.02)), and span length of the spatial-memory task (beta (95% CI): −0.01 (−0.02, −0.004)).

Summary

Medium and *high* confidence studies covering a range of exposure levels across diverse geographic regions and evaluating varying measures of developmental neurocognitive outcomes provide general consistency regarding the effect of arsenic on developmental neurocognition. A dose-response gradient was observed in some analyses [e.g., (Wasserman et al., 2004)]. There is coherence with the evidence of effects on social, behavioral, and emotional effects, motor effects, and developmental delays (described below). Some inconsistencies across the results reviewed in this section may be due in part to variations in the age of assessment of the exposure and outcome, though there are not sufficient data to confirm these explanations. There are also some unexplained inconsistencies. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.

Social, behavioral, and emotional effects

The systematic literature review identified 21 *medium* or *high* confidence epidemiological studies (see Figure 3-43) that evaluated the relationship between iAs and social, behavioral, and emotional effects in children. The studies primarily evaluated behavioral function and disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder-related behaviors, anxiety and depression, and personal-social development (see Figure 3-44).

Four of these were case-control studies examining the association between arsenic and autism spectrum disorder (ASD), (Skogheim et al., 2021; Rahbar et al., 2021; Nabgha-e-Amen et al., 2020; Adams et al., 2013). In the Norwegian Mother, Father and Child Cohort, authors observed increased odds of autism spectrum disorder in relation to the second quartile of As exposure from a GW 17 maternal blood sample (2nd quartile of exposure = 1.01–1.59 μg/L; OR = 1.77 (05% CI: 1.26–2.49)), (Skogheim et al., 2021). Similarly, a study from Pakistan observed a large association between arsenic in hair and ASD risk in children (OR: 18.29 (95% CI: 1.98, 169.05); mean: 0.33 μg/g hair in cases vs. 0.21 μg/g in controls) as well as with urinary arsenic (OR: 1.04 (95% CI: 1.01, 1.06); mean: 36.67 μg/g creatinine in cases vs. 15.65 μg/g creatinine in controls) (Nabgha-e-Amen et al., 2020). However, another study in Pakistan observed no statistically significant difference in adjusted geometric mean arsenic blood concentration for controls (1.29 μg/L) compared with autism cases (1.47 μg/L) (Rahbar et al., 2021). In the U.S., Adams et al. (2013) evaluated the association with autism in children 5–16 years of age; they found no significant difference in median arsenic levels in whole blood or urine between controls and cases (mean blood: ASD cases: 3.30 μg/L; controls: 3.37 μg/L; mean urine: ASD cases: 30.8 μg/g; 17.9 μg/g).

Twelve cross-sectional studies across different countries examined other behavioral, social and emotional effects in children (Vaidya et al., 2023; Stein et al., 2022; Roy et al., 2011; Rodríguez-Carrillo et al., 2022; Rodríguez-Barranco et al., 2016; Renzetti et al., 2021; Nahar et al., 2014b; Ma et al., 2023; Huang et al., 2023; Egwunye et al., 2022; Dai et al., 2023). Many studies reported positive or suggestive positive associations (i.e., more reported problems with higher exposures). For example, in a cross-sectional study in Spain, authors observed the second tertile of urinary arsenic (6.47–16.18 μg/g) to be associated with internalizing problems in children, including anxiety and somatic problems (beta (95% CI): internalizing problems: 5.87 (0.52, 11.22); anxious-depressed: 4.0 (0.87, 7.13); somatic complaints: 5.58 (1.66, 9.50) (Rodríguez-Carrillo et al., 2022). In a cross-sectional study in Italy, urinary arsenic (median: 8.3 μg/L) was associated with increased neurobehavioral problems, including anxious-depressed, somatic complaints, attention problems, and rule-breaking behavior (beta (95% CI): anxious-depressed: 0.8 (0.1, 1.5); somatic complaints: 1.5 (0.1, 2.9); attention problems: 0.9 (0.2, 1.7); rule-breaking behavior: 0.9 (0.2, 1.7)) (Renzetti et al., 2021). In Mexico, Roy et al. (2011) reported modest associations in a cross-sectional study using urinary arsenic levels (median of 55.2 μg/L) in students (6–8 years of age). Compared with the lowest quartile (7.7–35.9 μg/L) of urinary arsenic, those in the 2nd quartile (36–55 μg/L) had higher scores on the oppositional behavior rating (beta (95% CI): 3.1 (0.01, 6.1)), but effect

estimates in the higher quartiles overlapped with the null (Roy et al., 2011). In the United States, there were some associations between hair arsenic among 6- to 12-year-olds (median: 0.018 µg/g) and parent-reported ADHD-like behaviors (e.g., inattentive, hyperactive), though confidence intervals included the null (beta (95% CI); ADHD T-score: 1.14 (−0.4, 2.7); inattentive T-score: 1.02 (−0.4, 2.4); hyperactive T-score: 1.04 (−0.35, 2.43)) (Stein et al., 2022). Associations between urinary arsenic at 6–9 years (geometric mean: 0.70 µg/L) and ADHD-like behaviors were also observed in a cohort in Spain (beta (95% CI); impulsivity: 0.6 (0.1, 1.1); inattention: 0.5 (0.03, 1.0)) (Rodríguez-Barranco et al., 2016). However, some studies in Taiwan and China reported no significant associations between urinary arsenic at 3–6 years (mean in Taiwan: 102.1 µg/g creatinine; median in China: 33.86 µg/L −40.75 µg/g creatinine) and behavioral problems (Ma et al., 2023; Huang et al., 2023; Dai et al., 2023). Yet, in one of the studies based in China, urinary arsenic (median: 33.86 µg/L) was associated with anxious and depressed behavior scores among girls only (beta (95% CI): 0.71 (0.12, 2.31)) (Dai et al., 2023).

There were also seven prospective cohort analyses evaluating this association (Patti et al., 2022; Nyanza et al., 2021; Nozadi et al., 2021; Lozano et al., 2024; Liang et al., 2020; Karakis et al., 2021; Dai et al., 2023). Study results were overall mixed. In a prospective cohort in China (n = 2,315 mother-infant pairs), the status of children's development and behavior at 6 months postpartum was assessed in relation to cord serum arsenic levels (Liang et al., 2020). Compared with the low arsenic reference group (<1.27 µg/L), medium (1.27–2.89 µg/L) and high (>2.89 µg/L) arsenic groups were associated with increased risks of a 'significant development delay' in the personal-social domain among infants (OR (95% CI); medium group: 1.33 (1.01, 1.75); high group: 1.47 (1.08, 2.00)) (Liang et al., 2020). In Canada, first trimester urinary DMA concentrations (median: 2.23 µg/L) were associated with decreased odds of optimal neurodevelopment at 3 years of age (based on both cognitive and behavioral components), though the confidence interval included the null (OR (95% CI): 0.44 (0.19, 1.02) (Patti et al., 2022). Among a cohort in Spain, MMA averaged across the first and third trimesters (GM: 0.34 µg/g) was associated with increased total emotional and behavioral problems among children at 9 years of age (IRR (95% CI): 1.06 (1.01, 1.12)); results were attenuated for models based on total arsenic (GM: 49.59 µg/g) and iAs (GM: 0.32 µg/g) (IRR (95% CI); total arsenic: 1.01 (0.97, 1.04); iAs: 1.03 (0.98, 1.08)) (Lozano et al., 2024). However, some studies observed no associations. For example, a cohort study from Israel found no association between arsenic from a maternal urine sample collected prior to delivery (geometric mean: 3.59 ppb) and child behavioral disorders (Karakis et al., 2021). Similarly, a study in China did not observe associations between maternal urinary arsenic during pregnancy (median: 22.22 µg/L) and child behavioral problems at 6 years of age (Dai et al., 2023). In Tanzania, there was no association between prenatal total arsenic (median: 8.3 µg/L) and social development at 6–12 months of age.

Summary

There is *slight* evidence for an association between arsenic exposure and social, behavioral, and emotional effects based on 21 *medium* or *high* confidence studies across diverse geographic regions and using different types of exposure biomarkers. Four case-control studies examined autism, with unexplained inconsistency of findings across these studies. Thirteen cross-sectional, case-control, and cohort studies evaluated impacts on a variety of other behavioral and emotional endpoints. Many of these studies indicated associations or suggestive associations with arsenic; some of the variations in the evidence base may be due to the range of endpoints evaluated in this outcome category, though this explanation cannot be confirmed, and there may also be other unexplained considerations. There is coherence with the evidence bases for developmental neurocognitive effects and some of the evidence for motor effects and developmental delays. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.

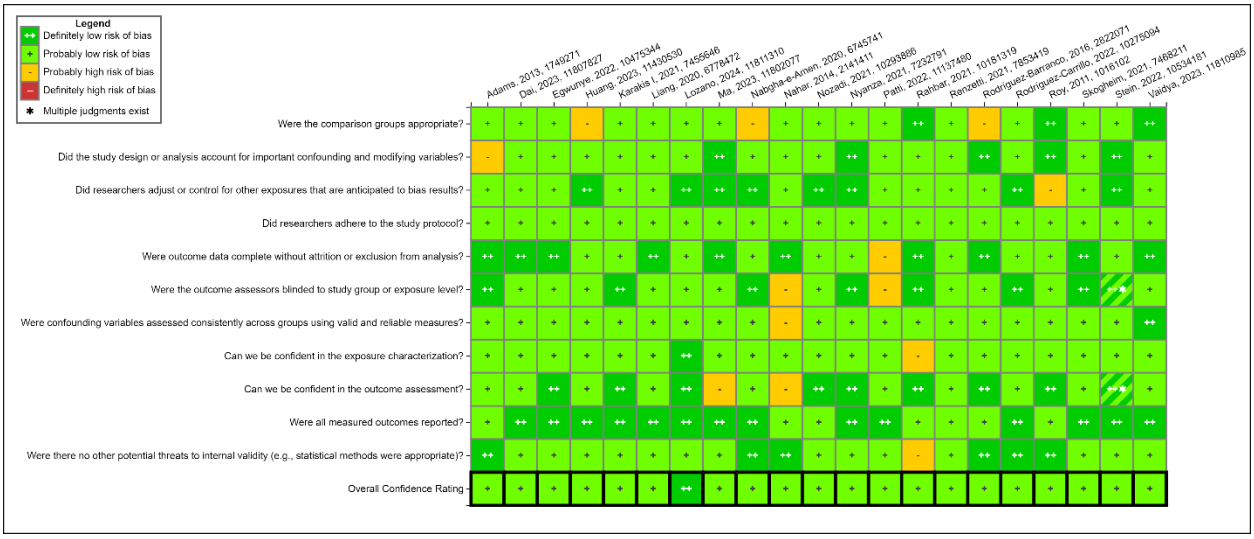
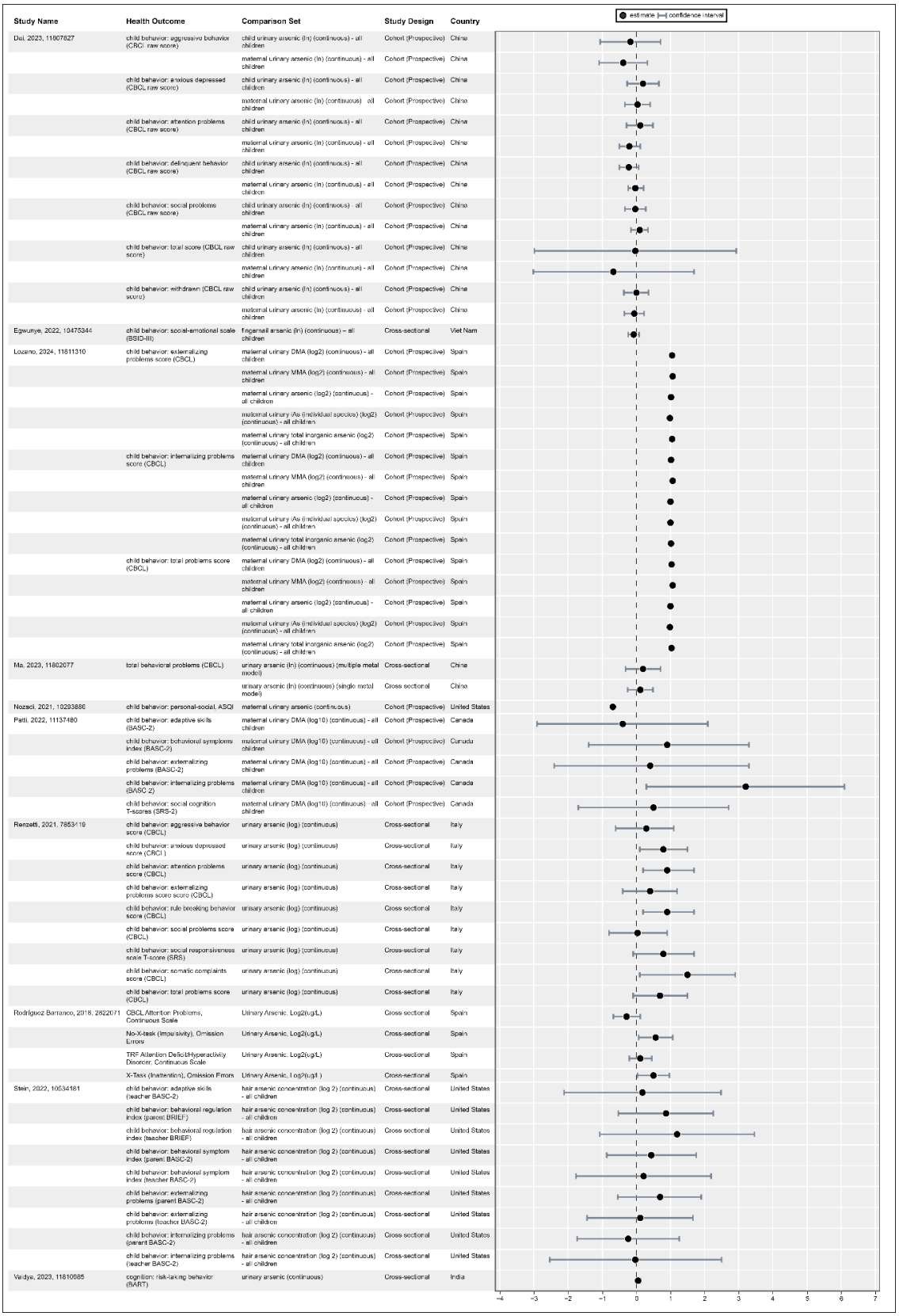
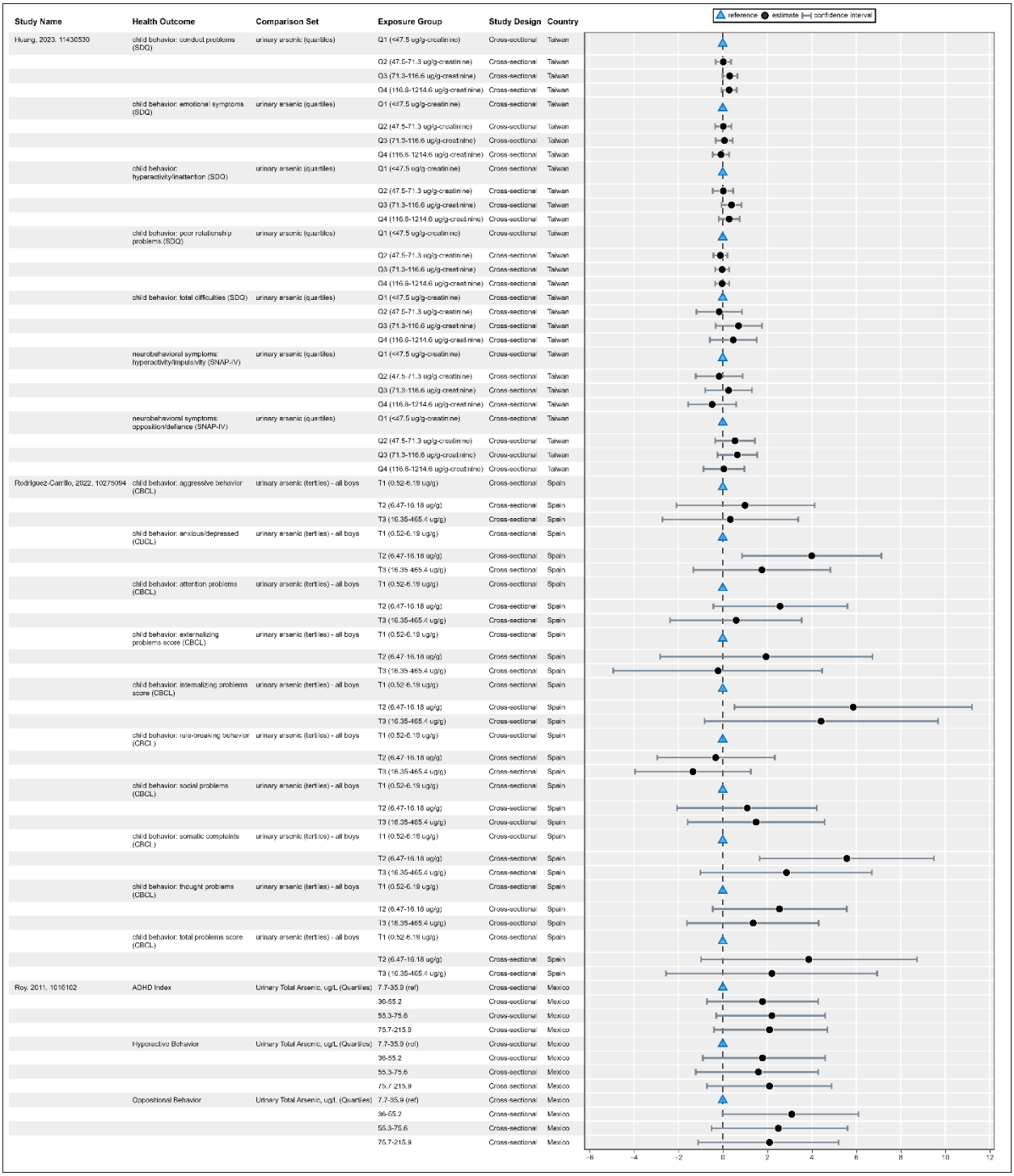


Figure 3-43. Study evaluation ratings for references evaluating social, behavioral, and emotional effects (see interactive version in HAWC).



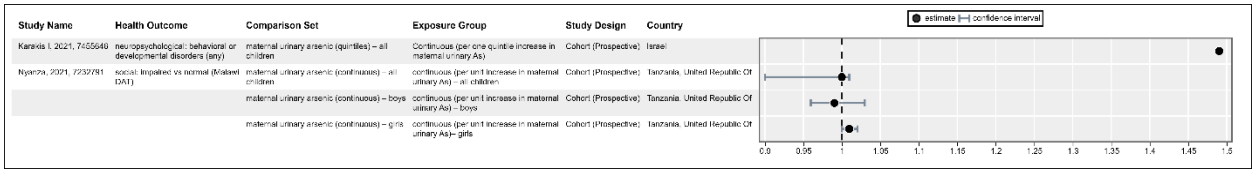
Study Name	Health Outcome	Comparison Set	Study Design	Country
Dai, 2023, 11807627	child behavior: aggressive behavior (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
	child behavior: anxious depressed (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
	child behavior: attention problems (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
	child behavior: delinquent behavior (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
	child behavior: social problems (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
	child behavior: total score (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
	child behavior: withdrawn (CBCL raw score)	child urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
		maternal urinary arsenic (ln) (continuous) - all children	Cohort (Prospective)	China
Egwunye, 2022, 10475344	child behavior: social-emotional scale (BSID-III)	fingernail arsenic (ln) (continuous) – all children	Cross-sectional	Viet Nam
Lozano, 2024, 11811310	child behavior: externalizing problems score (CBCL)	maternal urinary DMA (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary MMA (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary arsenic (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary iAs (individual species) (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary total inorganic arsenic (log2) (continuous) - all children	Cohort (Prospective)	Spain
	child behavior: internalizing problems score (CBCL)	maternal urinary DMA (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary MMA (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary arsenic (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary iAs (individual species) (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary total inorganic arsenic (log2) (continuous) - all children	Cohort (Prospective)	Spain
	child behavior: total problems score (CBCL)	maternal urinary DMA (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary MMA (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary arsenic (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary iAs (individual species) (log2) (continuous) - all children	Cohort (Prospective)	Spain
		maternal urinary total inorganic arsenic (log2) (continuous) - all children	Cohort (Prospective)	Spain
Ma, 2023, 11802077	total behavioral problems (CBCL)	urinary arsenic (ln) (continuous) (multiple metal model)	Cross-sectional	China
		urinary arsenic (ln) (continuous) (single metal model)	Cross sectional	China
Nozadi, 2021, 10293886	child behavior: personal-social, ASQ	maternal urinary arsenic (continuous)	Cohort (Prospective)	United States
Patil, 2022, 11137480	child behavior: adaptive skills (BASC-2)	maternal urinary DMA (log10) (continuous) - all children	Cohort (Prospective)	Canada
	child behavior: behavioral symptoms index (BASC-2)	maternal urinary DMA (log10) (continuous) - all children	Cohort (Prospective)	Canada
	child behavior: externalizing problems (BASC-2)	maternal urinary DMA (log10) (continuous) - all children	Cohort (Prospective)	Canada
	child behavior: internalizing problems (BASC 2)	maternal urinary DMA (log10) (continuous) - all children	Cohort (Prospective)	Canada
	child behavior: social cognition T-scores (SRS-2)	maternal urinary DMA (log10) (continuous) - all children	Cohort (Prospective)	Canada
Renzetti, 2021, 7853119	child behavior: aggressive behavior score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: anxious depressed score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: attention problems score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: externalizing problems score score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: rule breaking behavior score (CBCL)	urinary arsenic (log) (continuous)	Cross sectional	Italy
	child behavior: social problems score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: social responsiveness scale T-score (SRS)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: somatic complaints score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
	child behavior: total problems score (CBCL)	urinary arsenic (log) (continuous)	Cross-sectional	Italy
Rodríguez Barranco, 2018, 2822071	CBCL Attention Problems, Continuous Scale	Urinary Arsenic, Log2(ug/L)	Cross-sectional	Spain
	No-X-task (Impulsivity), Omission Errors	Urinary Arsenic, Log2(ug/L)	Cross-sectional	Spain
	TRF Attention Deficit/Hyperactivity Disorder, Continuous Scale	Urinary Arsenic, Log2(ug/L)	Cross-sectional	Spain
	X-Task (Inattention), Omission Errors	Urinary Arsenic, Log2(ug/l)	Cross-sectional	Spain
Stein, 2022, 10534181	child behavior: adaptive skills (teacher BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: behavioral regulation index (parent BRIEF)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: behavioral regulation index (teacher BRIEF)	hair arsenic concentration (log 2) (continuous) - all children	Cross sectional	United States
	child behavior: behavioral symptom index (parent BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: behavioral symptom index (teacher BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: externalizing problems (parent BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: externalizing problems (teacher BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: internalizing problems (parent BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
	child behavior: internalizing problems (teacher BASC-2)	hair arsenic concentration (log 2) (continuous) - all children	Cross-sectional	United States
Vaidya, 2023, 11810585	cognition: risk-taking behavior (BART)	urinary arsenic (continuous)	Cross-sectional	India

(a) Difference measures, biomarkers, continuous exposures



Study Name	Health Outcome	Comparison Set	Exposure Group	Study Design	Country
Huang, 2023, 11430530	child behavior: conduct problems (SDQ)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
	child behavior: emotional symptoms (SDQ)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
	child behavior: hyperactivity/inattention (SDQ)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
	child behavior: peer relationship problems (SDQ)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
	child behavior: total difficulties (SDQ)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
	neurobehavioral symptoms: hyperactivity/impulsivity (SNAP-IV)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
	neurobehavioral symptoms: opposition/defiance (SNAP-IV)	urinary arsenic (quartiles)	Q1 (<47.5 ug/g-creatinine)	Cross-sectional	Taiwan
			Q2 (47.5-71.3 ug/g-creatinine)	Cross-sectional	Taiwan
			Q3 (71.3-116.6 ug/g-creatinine)	Cross-sectional	Taiwan
			Q4 (116.6-1214.6 ug/g-creatinine)	Cross-sectional	Taiwan
Rodriguez-Carrillo, 2022, 10275094	child behavior: aggressive behavior (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: anxious/depressed (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: attention problems (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: externalizing problems score (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: internalizing problems score (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: rule-breaking behavior (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: social problems (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: somatic complaints (CBCL)	urinary arsenic (tertiles) - all boys	11 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: thought problems (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
	child behavior: total problems score (CBCL)	urinary arsenic (tertiles) - all boys	T1 (0.52-6.19 ug/g)	Cross-sectional	Spain
			T2 (6.47-16.18 ug/g)	Cross-sectional	Spain
			T3 (16.35-465.4 ug/g)	Cross-sectional	Spain
Roy, 2011, 1016102	ADHD Index	Urinary Total Arsenic, ug/L (Quartiles)	7.7-35.9 (ref)	Cross-sectional	Mexico
			36-55.2	Cross-sectional	Mexico
			55.3-75.6	Cross-sectional	Mexico
			75.7-215.9	Cross-sectional	Mexico
	Hyperactive Behavior	Urinary Total Arsenic, ug/L (Quartiles)	7.7-35.9 (ref)	Cross-sectional	Mexico
			36-55.2	Cross-sectional	Mexico
			55.3-75.6	Cross-sectional	Mexico
			75.7-215.9	Cross-sectional	Mexico
	Oppositional Behavior	Urinary Total Arsenic, ug/L (Quartiles)	7.7-35.9 (ref)	Cross-sectional	Mexico
			36-55.2	Cross-sectional	Mexico
			55.3-75.6	Cross-sectional	Mexico
			75.7-215.9	Cross-sectional	Mexico

(b) Difference measures, biomarkers, categorical exposures



(c) Ratio measures, biomarkers, continuous exposures

Figure 3-44. Thumbnail schematic of studies addressing the association between inorganic arsenic exposure and social, behavioral, and emotional effects (a) difference measures, biomarkers, continuous exposures; (b) difference measures, biomarkers, categorical exposures; (c) ratio measures, biomarkers, continuous exposures (see interactive data graphic).

Motor effects

Fifteen *medium* and *high* confidence studies, using four different exposure measures, examined motor functions and skills across diverse areas (such as Bangladesh, Nepal, Vietnam, United States, Spain, China, and Taiwan) (Tofail et al., 2009; Soler-Blasco et al., 2022; Signes-Pastor et al., 2019b; Parvez et al., 2011; Parajuli et al., 2014; Parajuli et al., 2015b; Parajuli et al., 2015a; Nyanza et al., 2021; Nozadi et al., 2021; Kao et al., 2023a; Jiang et al., 2022; Hamadani et al., 2010; Egwunye et al., 2022; Chen et al., 2023; Butler et al., 2023) (see Figure 3-45 and Figure 3-46).

Five of these studies were cross-sectional (Signes-Pastor et al., 2019b; Parvez et al., 2011; Kao et al., 2023a; Jiang et al., 2022; Egwunye et al., 2022). Most of these studies documented adverse effects on motor function. For example, one study investigated the association between arsenic and motor coordination in children aged 8–11 years in Bangladesh through various endpoints including body coordination, manual coordination, fine manual control, and strength and agility (Parvez et al., 2011). The authors observed inverse associations between total motor composite and body coordination scores and arsenic levels in drinking water (mean: 43.3 µg/L; beta (95% CI): body coordination (BC): −0.43 (−0.77, −0.06); total motor composite (TMC): −1.18 (−2.13, −0.10)), blood (mean: 4.8 µg/L; beta (95% CI); BC: −1.61 (−2.70, −0.51); TMC: −3.63 (−6.72, −0.54)), toenails (mean: 5.9 µg/g; beta (95% CI); BC: −1.86 (−2.83, −0.89); TMC: −3.77 (−6.52, −1.03)), and urine (mean: 246.5 µg/g creatinine; beta (95% CI); BC: −1.60 (−2.61, −0.60); TMC: −3.42 (−6.27, −0.57)) (Parvez et al., 2011). In Spain, authors observed inverse associations between several motor function scores and arsenic in urine among 4–5 year-olds (mean urinary arsenic levels: 4.85 µg/L; beta (95% CI): global score: −2.29 (−3.95, −0.63); gross score: −1.92 (−3.52, −0.31); fine score: −1.54 (−3.06, −0.03)) (Signes-Pastor et al., 2019b). Two studies of 2–3-year-olds from Taiwan observed that hair arsenic (median: 0.19 µg/g) or fingernail arsenic (central tendency not reported) were inversely associated with gross motor development [beta (95% CI): −0.032 (−0.061, −0.004) (Jiang et al., 2022)]; [beta (95% CI): −1.31 (−2.43, −0.19) (Kao et al., 2023a)]. However, in Vietnam, no significant association was observed between fingernail arsenic (median (IQR) = 0.4 (0.3–0.5) µg/g) and motor skills (Egwunye et al., 2022).

There were also 10 cohort studies that evaluated the impact of arsenic on motor function (Tofail et al., 2009; Soler-Blasco et al., 2022; Parajuli et al., 2014; Parajuli et al., 2015b; Parajuli et al., 2015a; Nyanza et al., 2021; Nozadi et al., 2021; Hamadani et al., 2010; Chen et al., 2023; Butler et al., 2023). Results were overall mixed, though some of the inconsistencies may be due to differences in timing of exposure or outcome ascertainment.

Three studies evaluated psychomotor development among a cohort in Nepal (Parajuli et al., 2014; Parajuli et al., 2015b; Parajuli et al., 2015a). These studies estimated *in utero* exposure using arsenic levels in cord blood (mean 1.33 µg/L) and assessed psychomotor development at 6 months (Parajuli et al., 2014), 24 months (Parajuli et al., 2015a), and 36 months of age (Parajuli et al., 2015b). While no statistically significant association was found between arsenic exposure in cord blood at delivery and psychomotor development at any time point, the earlier study documented suggestive inverse associations (beta (95% CI): −2.02 (−13.02, 8.98) (Parajuli et al., 2014), while the two later studies documented suggestive positive associations (beta (95% CI); 24 months: 5.51 (−13.60, 24.62); 36 months: 6.25 (−5.08, 17.58)) (Parajuli et al., 2015b; Parajuli et al., 2015a). Maternal arsenic methylation, which results in lower exposure of toxic metabolites to the fetus, increases with advancing gestation (Section 1.5.1), which may partially explain these inconclusive results for late pregnancy exposure.

In Bangladesh, two studies evaluated high-level arsenic exposure and motor impacts using a cohort of pregnant women enrolled in the Maternal and Infant Nutritional Intervention at Matlab (MINIMat) study (Tofail et al., 2009; Hamadani et al., 2010). Tofail et al. (2009) assessed psychomotor development in infants (mean age 7.4 months) in relation to *in utero* arsenic exposure using maternal urinary arsenic levels at gestational week (GW) 8 and 30 (median: 81 and 84 µg/L, respectively). These exposure windows capture both early and late pregnancy. The authors found suggestive positive associations with psychomotor development, though confidence intervals included the null (beta (95% CI): 0.9 (−0.9, 2.7)) (Tofail et al., 2009). A follow-up study by Hamadani et al. (2010) assessed psychomotor development in infants 18 months of age and documented slight inverse and slight positive associations of psychomotor development with infant urinary arsenic levels (mean: 34.6 µg/L) and maternal urinary arsenic levels (mean: 96.3 µg/L), respectively, though confidence intervals included the null (beta (95% CI); child urine: −0.07 (−1.5, 1.3); maternal urine: 0.3 (−1.3, 1.9)) (Hamadani et al., 2010). For both of these studies, the authors posited that the impacts of exposure may become more apparent at later ages.

In a cohort based in China, there were no associations between iAs during pregnancy (average GM across three trimesters: 3.26 µg/L) and fine and gross motor development (Chen et al., 2023). And in a cohort based in Tanzania, second trimester total urinary arsenic (median: 8.3 µg/L) was not associated with abnormal fine or gross motor development (Nyanza et al., 2021). However, among a cohort based in the United States, total urinary arsenic at 24–28 weeks gestation (second trimester) (median: 4.0 µg/L), was associated with decrements in motor development (linear model beta (95% CI); short form: −0.77 (−1.42, −0.13); fine motor integration: −0.23 (−0.62, 0.15);

change-point model beta (95% CI); short form: −3.25 (−6.09, −0.40); fine motor integration: −4.29 (−7.95, −0.63)) (Butler et al., 2023).

Summary

From 15 *medium* and *high* confidence studies from diverse regions, many studies provide evidence of adverse or suggestive adverse motor effects. Some of the observed inconsistencies may be due to differences in the timing of exposure or outcome assessment, though this explanation cannot be confirmed. There may also be other unexplained factors. There is coherence with the evidence for developmental neurocognitive effects and some of the evidence for social, behavioral, and emotional effects and developmental delays. There is some imprecision in the observed results, as some studies have large confidence intervals that include the null.

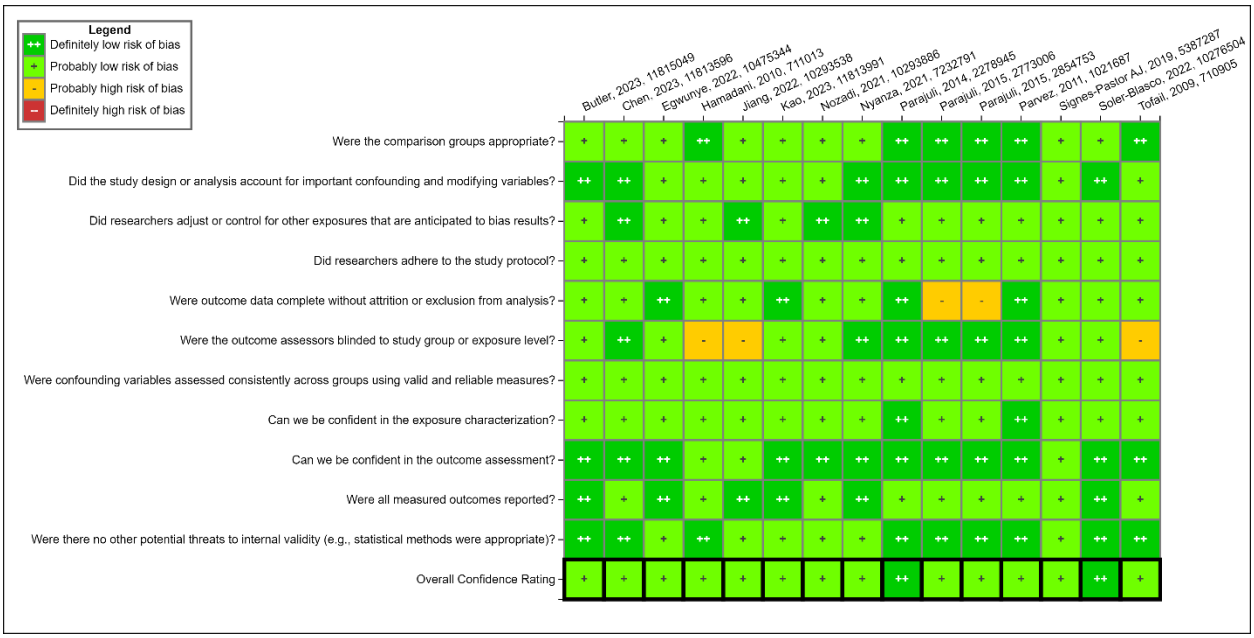
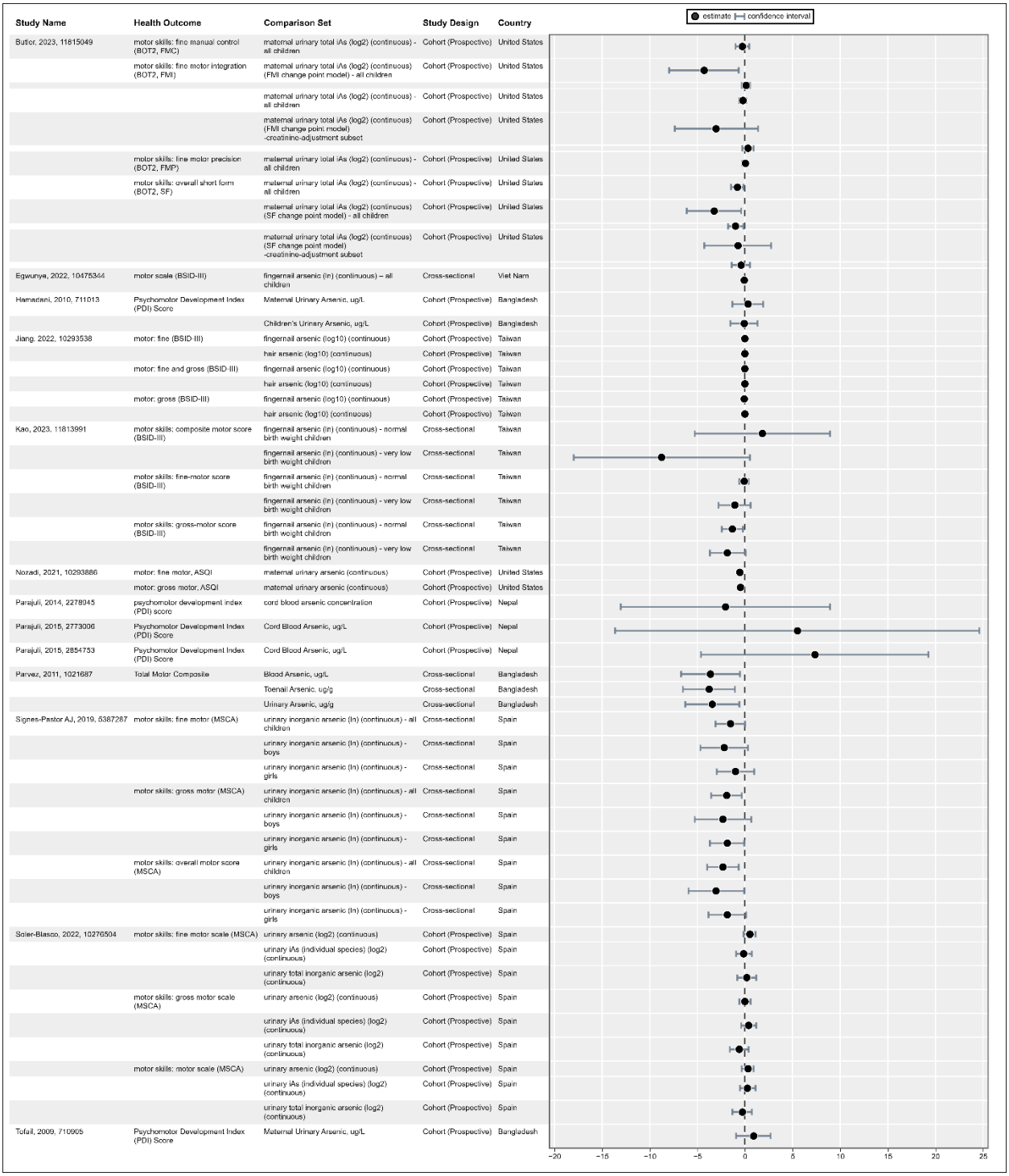


Figure 3-45. Study evaluation ratings for references evaluating motor effects (see interactive version in HAWC).



Study Name	Health Outcome	Comparison Set	Study Design	Country
Butler, 2023, 11815049	motor skills: fine manual control (BOT2, FMC)	maternal urinary total iAs (log2) (continuous) - all children	Cohort (Prospective)	United States
	motor skills: fine motor integration (BOT2, FMI)	maternal urinary total iAs (log2) (continuous) (FMI change point model) - all children	Cohort (Prospective)	United States
		maternal urinary total iAs (log2) (continuous) - all children	Cohort (Prospective)	United States
		maternal urinary total iAs (log2) (continuous) (FMI change point model) -creatinine-adjustment subset	Cohort (Prospective)	United States
	motor skills: fine motor precision (BOT2, FMP)	maternal urinary total iAs (log2) (continuous) - all children	Cohort (Prospective)	United States
	motor skills: overall short form (BOT2, SF)	maternal urinary total iAs (log2) (continuous) - all children	Cohort (Prospective)	United States
		maternal urinary total iAs (log2) (continuous) (SF change point model) - all children	Cohort (Prospective)	United States
		maternal urinary total iAs (log2) (continuous) (SF change point model) -creatinine-adjustment subset	Cohort (Prospective)	United States
Egwunya, 2022, 10475344	motor scale (BSID-III)	fingernail arsenic (ln) (continuous) – all children	Cross-sectional	Viet Nam
Hamadani, 2010, 711013	Psychomotor Development Index (PDI) Score	Maternal Urinary Arsenic, ug/L	Cohort (Prospective)	Bangladesh
		Children's Urinary Arsenic, ug/L	Cohort (Prospective)	Bangladesh
Jiang, 2022, 10293538	motor: fine (BSID-III)	fingernail arsenic (log10) (continuous)	Cohort (Prospective)	Taiwan
		hair arsenic (log10) (continuous)	Cohort (Prospective)	Taiwan
	motor: fine and gross (BSID-III)	fingernail arsenic (log10) (continuous)	Cohort (Prospective)	Taiwan
		hair arsenic (log10) (continuous)	Cohort (Prospective)	Taiwan
	motor: gross (BSID-III)	fingernail arsenic (log10) (continuous)	Cohort (Prospective)	Taiwan
		hair arsenic (log10) (continuous)	Cohort (Prospective)	Taiwan
Kao, 2023, 11813991	motor skills: composite motor score (BSID-III)	fingernail arsenic (ln) (continuous) - normal birth weight children	Cross-sectional	Taiwan
		fingernail arsenic (ln) (continuous) - very low birth weight children	Cross-sectional	Taiwan
	motor skills: fine-motor score (BSID-III)	fingernail arsenic (ln) (continuous) - normal birth weight children	Cross-sectional	Taiwan
		fingernail arsenic (ln) (continuous) - very low birth weight children	Cross-sectional	Taiwan
	motor skills: gross-motor score (BSID-III)	fingernail arsenic (ln) (continuous) - normal birth weight children	Cross-sectional	Taiwan
		fingernail arsenic (ln) (continuous) - very low birth weight children	Cross-sectional	Taiwan
Nozadi, 2021, 10293886	motor: fine motor, ASQI	maternal urinary arsenic (continuous)	Cohort (Prospective)	United States
	motor: gross motor, ASQI	maternal urinary arsenic (continuous)	Cohort (Prospective)	United States
Parajuli, 2014, 2278945	psychomotor development index (PDI) score	cord blood arsenic concentration	Cohort (Prospective)	Nepal
Parajuli, 2015, 2773006	Psychomotor Development Index (PDI) Score	Cord Blood Arsenic, ug/L	Cohort (Prospective)	Nepal
Parajuli, 2015, 2854753	Psychomotor Development Index (PDI) Score	Cord Blood Arsenic, ug/L	Cohort (Prospective)	Nepal
Parvez, 2011, 1021687	Total Motor Composite	Blood Arsenic, ug/L	Cross-sectional	Bangladesh
		Toenail Arsenic, ug/g	Cross-sectional	Bangladesh
		Urinary Arsenic, ug/g	Cross-sectional	Bangladesh
Signes-Pastor AJ, 2019, 5387287	motor skills: fine motor (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	Cross-sectional	Spain
		urinary inorganic arsenic (ln) (continuous) - boys	Cross-sectional	Spain
		urinary inorganic arsenic (ln) (continuous) - girls	Cross-sectional	Spain
	motor skills: gross motor (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	Cross-sectional	Spain
		urinary inorganic arsenic (ln) (continuous) - boys	Cross-sectional	Spain
		urinary inorganic arsenic (ln) (continuous) - girls	Cross-sectional	Spain
	motor skills: overall motor score (MSCA)	urinary inorganic arsenic (ln) (continuous) - all children	Cross-sectional	Spain
		urinary inorganic arsenic (ln) (continuous) - boys	Cross-sectional	Spain
		urinary inorganic arsenic (ln) (continuous) - girls	Cross-sectional	Spain
Soler-Blasco, 2022, 10276504	motor skills: fine motor scale (MSCA)	urinary arsenic (log2) (continuous)	Cohort (Prospective)	Spain
		urinary iAs (individual species) (log2) (continuous)	Cohort (Prospective)	Spain
		urinary total inorganic arsenic (log2) (continuous)	Cohort (Prospective)	Spain
	motor skills: gross motor scale (MSCA)	urinary arsenic (log2) (continuous)	Cohort (Prospective)	Spain
		urinary iAs (individual species) (log2) (continuous)	Cohort (Prospective)	Spain
		urinary total inorganic arsenic (log2) (continuous)	Cohort (Prospective)	Spain
	motor skills: motor scale (MSCA)	urinary arsenic (log2) (continuous)	Cohort (Prospective)	Spain
		urinary iAs (individual species) (log2) (continuous)	Cohort (Prospective)	Spain
		urinary total inorganic arsenic (log2) (continuous)	Cohort (Prospective)	Spain
Tofail, 2009, 710905	Psychomotor Development Index (PDI) Score	Maternal Urinary Arsenic, ug/L	Cohort (Prospective)	Bangladesh

Figure 3-46. Thumbnail schematic of studies addressing the association between inorganic arsenic exposure and motor effects: difference measures, biomarkers, continuous exposures (see interactive data graphic).

Developmental delays

There were three *medium* confidence studies based in Taiwan that evaluated general developmental delays, composed of components across cognitive, social/behavioral/emotional, and motor domains, in relation to arsenic exposure (see Figure 3-47 and Figure 3-48). In a cross-sectional study of children in Taiwan, paternal and maternal toenail arsenic levels (median: 0.11–0.15 µg/g) but not child toenail arsenic (median: 0.19–0.22 µg/g) were associated with suspected developmental delays (beta (95% CI); paternal toenail: 13.52 (2.31, 78.94); maternal toenail: 5.09 (1.40, 18.41)) (Kao et al., 2023b). There were also two case-control studies from Taiwan evaluating this question. Hsieh et al. (2014) compared mean total urinary arsenic levels in children aged 4–6 years with (19.7 µg/L) and without (10.2 µg/L) developmental delays. Children in the highest tertile of arsenic exposure (total arsenic >24.7 µg/g creatinine) had an increased odds of developmental delay (OR (95% CI): 11.83 (1.52, 91.82)) (Hsieh et al., 2014). Similar results were obtained in a more recent study of children with and without developmental delay (third tertile (>18.46 µg/L) OR (95% CI): 2.67 (1.05, 6.77)) (Hsueh et al., 2022). Both of the case-control studies suggest a dose-response gradient (Hsueh et al., 2022; Hsieh et al., 2014).

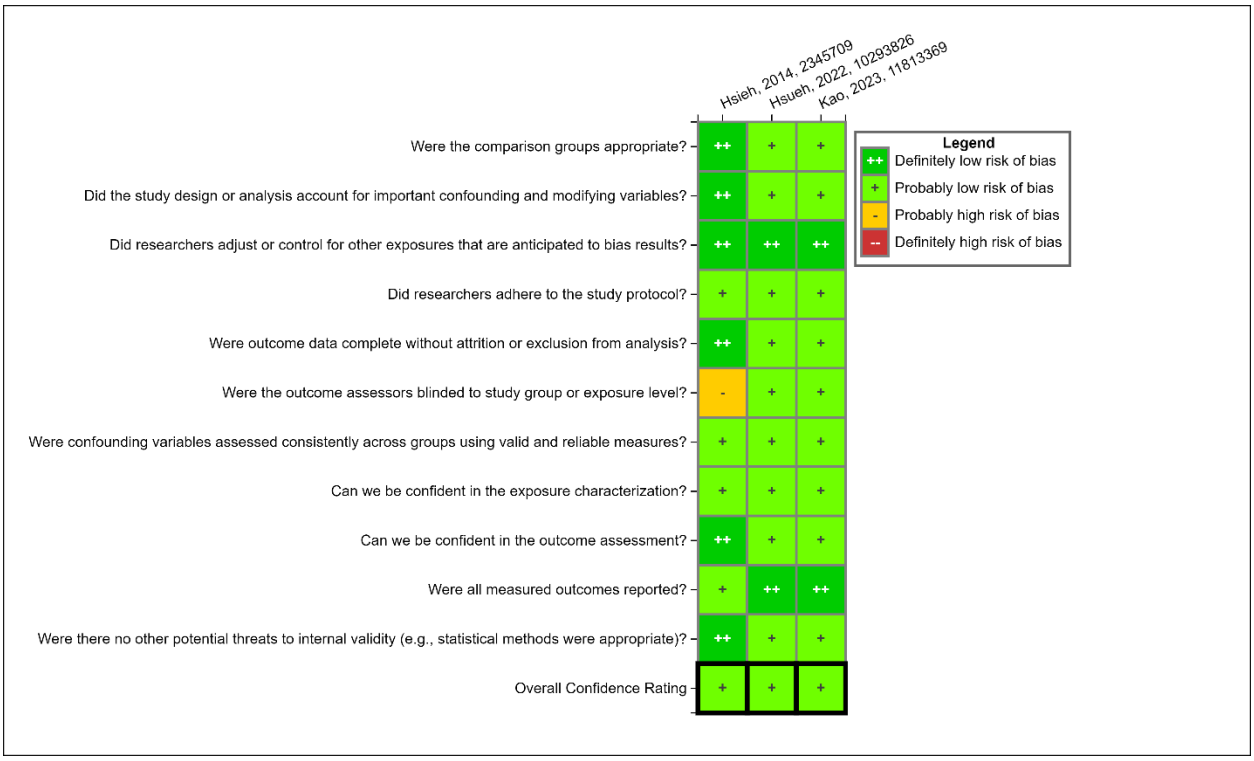


Figure 3-47. Study evaluation ratings for references evaluating developmental delays (see interactive version in HAWC).

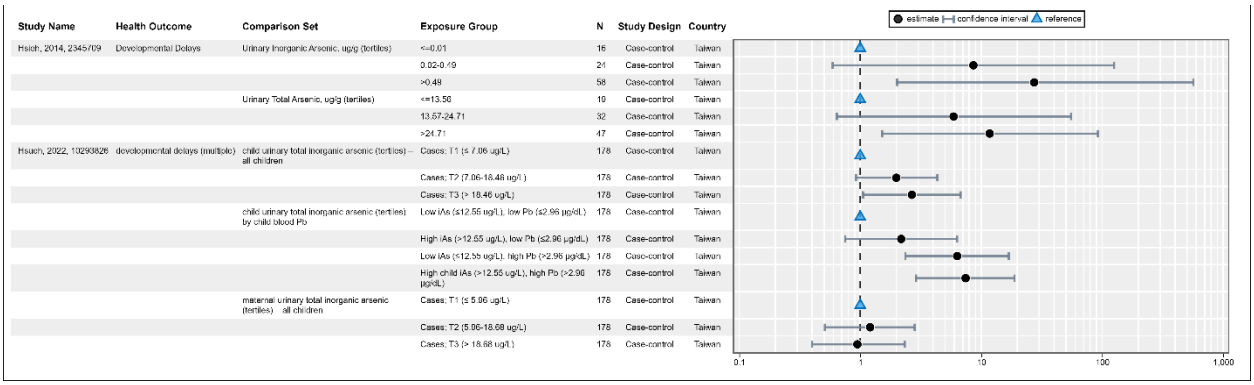


Figure 3-48. Thumbnail schematic of studies addressing the association between inorganic arsenic exposure and developmental delays: difference measures, biomarkers, continuous exposures (see interactive data graphic).

Mechanistic Observations and Biological Plausibility

Researchers have proposed several potential mechanisms for a possible association between iAs and neurodevelopmental effects. Herrera et al. (2013) showed that oral administration of arsenic to mice at 50,000 µg/L was consistent with increased oxidative stress in the brain, resulting in reduced levels of glutathione and increased lipid peroxidation, which could lead to neurodevelopmental effects. Other studies have explored arsenic interaction with hormone binding domains such as the glucocorticoid receptor [GR]. Several studies suggest that alterations in GR transcription are linked to subsequent changes in hypothalamic-pituitary-adrenal [HPA] axis activity. The HPA axis is a major part of the neuroendocrine system; prenatal and early life stressors on this system have been shown to be associated with findings of developmental neurotoxicity (e.g., impaired stress response, depressive-like behaviors) following developmental iAs exposure in mice (Goggin et al., 2012; Martinez-Finley et al., 2011; Martinez-Finley et al., 2009; Martinez et al., 2008). The results observed in rodents suggesting that endocrine effects may result in developmental neurotoxicity are concordant with findings in the epidemiologic literature that show a correlation between early life exposure to iAs and impaired cognitive function (Wasserman et al., 2007).

Other studies in rats suggest that exposure to iAs could result in changes in the brain, such as the increased expression of neural cell adhesion molecules (Luo et al., 2013) or damage to nerve fiber tracts, including discontinued axons (Ríos et al., 2009). These are likely to be secondary events. However, it is possible that hormonal interactions—particularly with estrogen and thyroid hormones, which are essential for brain development—also could be responsible for the iAs-related changes in the developing brain (Hamadani et al., 2011). Overall, the specific underlying mechanism(s) by which iAs may be producing the observed adverse neurodevelopmental effects is yet to be fully elucidated.

As discussed above inorganic arsenic exposure has been associated with developmental neurotoxicity, specifically decreased cognitive and IQ in young children. Evidence from

neurodevelopmental studies show that mice perinatally exposed to low levels of inorganic arsenic (50 ppb) exhibited dysregulation of the hypothalamic-pituitary-axis (HPA) (Martinez et al., 2008; Goggin et al., 2012). The HPA axis is a major part of the neuroendocrine system; prenatal and early life stressors on this system have been shown to be associated with findings of developmental neurotoxicity (e.g., impaired stress response, depressive-like behaviors) following developmental iAs exposure in mice 50 ppb (Martinez et al., 2008; Goggin et al., 2012). One component of the HPA axis is the corticosterone receptor (CR). These receptors are located in the hippocampus, amygdala, and lateral septum of the brain. The CR binds to corticosteroid hormones like cortisol and stimulates gene expression within brain cells impacting stress response, learning and memory. Martinez et al. (2008) showed that mice exposed to 50 ppb iAs prenatally displayed altered hippocampal CR, elevated serum corticosterone levels, and dysregulation of serotonin levels. Follow-up studies by this group showed that prenatally iAs exposed mice had fewer number of CR in the hippocampus versus control and displayed deficiencies in learning and memory (Martinez-Finley et al., 2009; Martinez-Finley et al., 2011). The evidence base demonstrates that moderate exposures to perinatal iAs can have adverse effects on learning, memory, and behavior (Martinez-Finley et al., 2009; Martinez-Finley et al., 2011; Martinez et al., 2008; Goggin et al., 2012) and provides biological plausibility to support the findings in the epidemiologic literature that show a correlation between early life exposure to iAs and deficiencies in cognitive development.

Risk Modifiers

A review of the epidemiological studies discussed in this section, along with studies identified from a targeted literature search (see Section 3.10 of iAs Protocol) on modifying factors identified in Table 3-8, suggest that the following factors increase the risk of arsenic-associated neurodevelopmental effects:

- **Environmental co-exposures:** Evidence is suggestive that co-exposures to lead result in an increased risk for neurodevelopmental effects in children, which might be expected as lead also is known to cause neurodevelopmental effects in children. Marlowe et al. (1985) and McDermott et al. (2011) indicate an interaction between arsenic and lead on neurodevelopmental effects, but neither indicates if the results are additive or greater than additive.

- **Sex:** Evidence is suggestive that sex may modify risk of neurodevelopmental effects. Some studies indicate that boys may be more susceptible to neurodevelopmental effects (Signes-Pastor et al., 2019b; Rosado et al., 2007), while others indicate that girls may be more susceptible (Wang et al., 2022b; Hamadani et al., 2011; Dai et al., 2023). In particular, girls appear to be more susceptible to impacts on measures of verbal IQ (Wang et al., 2022b; Hamadani et al., 2011).

Table 3-8. Risk modifiers for neurodevelopmental effects (selected study examples)

Risk modifiers	References	Finding	Population, exposure level
Environmental co-exposures	Marlowe et al. (1985)	Combination of arsenic and lead resulted in increased measures of acting out, disturbed peer relations, and immaturity in school-aged children	United States: 2.94 ppm (mean arsenic, hair); 6.65 ppm (mean lead, hair)
	Wasserman et al. (2011)	Combination of arsenic and manganese not related to decreased scores on intellectual function in school-aged children	Bangladesh: 117.8 µg/L (mean, water)
	Mcdermott et al. (2011)	Combination of arsenic and lead resulted in increased probability of intellectual disabilities in normal weight for gestational-aged infants	United States: 2.6 mg/kg (mean arsenic, soil); 35.4 mg/kg (mean lead, soil)
Sex	Rosado et al. (2007)	In tests related to problem solving and vocabulary, significant inverse associations were observed in boys but not girls	Mexico: 58.1 µg/L (mean, urine)
	Hamadani et al. (2011);	Decrease in full-scale and verbal IQ in girls; low and non-statistically significant associations in boys	Bangladesh: 51 µg/L (median, urine)
	Signes-Pastor et al. (2019b)	Suggestive inverse associations with scores in the quantitative index and working memory function among boys only. Inverse associations for overall motor score among boys, with attenuated suggestive inverse associations among girls	Spain: 4.85 µg/L (median, urine)
	Wang et al. (2022b)	Stronger and statistically significant impacts on verbal intelligence quotient among girls, especially at lower exposure levels	China: 1.64 µg/L (median, cord blood)
	Dai et al. (2023)	Urinary arsenic was associated with anxious and depressed behavior scores among girls only	China: 33.86 µg/L (median, urine)

Evidence Judgment

Across the body of evidence for neurodevelopmental effects, the currently available **evidence indicates** that iAs exposure likely causes neurodevelopmental effects in humans (see

Table 3-9) given sufficient exposure conditions.[23] This conclusion is based on studies of humans that assessed exposure levels much lower than 100 µg/L (e.g., including <20 µg/L) primarily showing developmental neurocognitive effects and, to a lesser extent, social, behavioral, and emotional effects. (Supplemental figures of results from studies documenting adverse effects from exposure to inorganic arsenic in drinking water at concentrations less than or equal to 100 µg/L, as described in 1.6.3, are available in Appendix B.5.) Human studies assessing susceptible populations and modifying factors provide evidence that early-life exposure to arsenic and co-exposures to lead might increase susceptibility to arsenic-associated neurodevelopmental effects.

There is *moderate* evidence supporting an association between arsenic and developmental neurocognitive effects that comes from 45 *medium* or *high* confidence epidemiological studies. There is general *consistency* for inverse associations between arsenic exposure and childhood cognitive measures across diverse geographic locations covering a range of exposure levels and using various outcome and exposure metrics. Some of these studies found evidence of associations with generally low concentrations of arsenic (e.g., <100 µg/L arsenic in drinking water, but also including <20 µg/L in drinking water [e.g., (Wasserman et al., 2014)]. There is *coherence* with some of the evidence of effects on social, behavioral, and emotional effects, motor effects, and developmental delays. Some inconsistencies across these developmental neurocognitive effects studies may be due in part to variations in the age of assessment of the exposure and outcome, though this explanation cannot be confirmed. There may be other *unexplained inconsistencies*. There is some *imprecision* in the observed results, as some studies have large confidence intervals that include the null.

There is *slight* evidence for an association between arsenic exposure and social, behavioral, and emotional effects based on 21 *medium* or *high* confidence studies across diverse geographic regions and using different types of exposure biomarkers. Four case-control studies examined autism, with *unexplained inconsistency* of findings across these studies. Fourteen cross-sectional and cohort studies of other behavioral and emotional endpoints provide some evidence of adverse or suggestive adverse effects of arsenic, though there is also some *unexplained inconsistency*. There is *coherence* with the evidence for developmental neurocognitive effects and some of the evidence for motor effects as well as general developmental delays. There is some *imprecision* in the observed results, as some studies have large confidence intervals that include the null. There is *slight* evidence for an association between arsenic exposure and motor effects based on 15 *medium* or *high* confidence studies. Some studies examining populations in different countries representing a range of exposure levels and using varied exposure and outcome assessment metrics report adverse or suggestive adverse effects. Some differences in results may be due to timing of exposure or outcome ascertainment, though this explanation cannot be confirmed. There may be other *unexplained inconsistency*. There is *coherence* with the evidence for developmental neurocognitive

[23]The term, "sufficient exposure conditions," is discussed and defined for the identified health effects in the dose-response analysis in Section 4.

effects and some of the evidence for social, behavioral, and emotional effects as well as developmental delays. There is some *imprecision* in the observed results, as some studies have large confidence intervals that include the null.

There is *slight* evidence for an association between arsenic exposure and developmental delays based on three *medium* or *high* confidence studies. Two of these studies provide evidence of a dose-response gradient (Hsueh et al., 2022; Hsieh et al., 2014). There is *coherence* with the evidence for developmental neurocognitive effects and some of the evidence for social, behavioral, and emotional effects and motor effects. There is some *imprecision* in the observed results, as some studies have large confidence intervals that include the null.

Overall, the currently available **evidence indicates** that iAs exposure likely causes neurodevelopmental effects in humans given sufficient exposure conditions. This conclusion is based on studies of humans that assessed exposure levels of <100 μg/L (including <20 μg/L) primarily showing developmental neurocognitive effects, and, to a lesser degree, social, behavioral, and emotional effects, motor effects, and developmental delays. Therefore, developmental neurocognitive effects will be considered for dose-response analysis (see Section 4.5).

Table 3-9. Evidence profile table for epidemiological evidence on iAs and neurodevelopmental effects

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
Studies	**Summary of key findings**	**Factors that increase certainty**	**Factors that decrease certainty**	**Evidence synthesis judgment(s)**
Developmental neurocognitive deficits 45 *medium or high* confidence studies	Evidence from studies of varying design (cohort, cross-sectional, cohort) evaluating populations chronically exposed to a range of arsenic levels, report generally consistent evidence of cognitive deficits across diverse populations and with a variety exposure and outcome assessment methods.	• Studies are *medium* or *high* confidence. • Consistency – across multiple geographic regions, exposure assessment metrics, and outcome metrics • Coherence – with some evidence from social, behavioral, and emotional effects; motor effects; and developmental delays	• Imprecision – some studies with large confidence intervals including the null • Unexplained inconsistency –for some studies in the evidence base	⊕⊕⊙ *Moderate*
Social, behavioral, and emotional effects 21 *medium* or *high* confidence studies	Two of four case-control studies identified an association with autism. With regard to other behavioral and emotional endpoints, varied study designs across different populations observed some associations with both internalizing and externalizing behaviors.	• Studies are *medium* or *high* confidence. Coherence – with developmental neurocognitive and some evidence from motor effects and developmental delays	• Unexplained inconsistency –for some studies in the evidence base • Imprecision – some studies with large confidence intervals including the null	⊕⊙⊙ *Slight*

Evidence stream summary and interpretation				
Evidence from studies of exposed humans				
Motor effects 15 *medium* or *high* confidence studies	Most studies from diverse regions covering a range of exposure levels identified an association between arsenic and adverse effects on motor skills and scores.	• Studies are *medium* or *high* confidence. Coherence – with developmental neurocognitive effects and some evidence from social, behavioral, and emotional effects; and developmental delays	• Unexplained inconsistency –for some studies in the evidence base • Imprecision – some studies with large confidence intervals including the null	⊕⊙⊙ *Slight*
Developmental delays 3 *medium* or *high* confidence studies	A small evidence base of studies using nail and urinary biomarkers in Taiwan identifies associations between arsenic exposure and developmental delays.	• Studies are *medium* or *high* confidence. • Dose-response gradient – observed in two of three studies. • Coherence – with developmental neurocognitive effects and some evidence from social, behavioral, and emotional effects and motor effects	• Imprecision – some studies with large confidence intervals including the null	⊕⊙⊙ *Slight*

3.3. HAZARD CONSIDERATIONS FOR DOSE-RESPONSE ANALYSIS

To address the extensive arsenic evidence base, an exposure-response screening-level approach was developed (Hobbie et al., 2020) and applied to available dose-response data sets to help prioritize health outcomes for hazard identification and dose-response analysis. The results of the screening-level analysis provided relative risk estimates for a broad set of health outcomes potentially useful for cost-benefit considerations in addition to identifying those endpoints that support multiple-study dose-response meta-analyses. Screening-level analyses identified diseases of the circulatory system (DCS) and diabetes as health effects with sufficient data for further analysis using the Bayesian dose-response meta-analysis approach. Diabetes, fetal, newborn, and infant health outcomes, and neurodevelopmental effects were also considered for further analysis based on those endpoints' utility for cost-benefit analyses that could be performed by EPA. As the result of this screening analysis of NRC Tier 1 and Tier 2 adverse health outcomes [see Section 5.1 of the Protocol, link provided in Appendix A and (NASEM, 2019)], EPA ultimately decided to focus on six adverse health outcomes for hazard identification and dose-response analysis in this assessment. Table 3-10 lists these six adverse health outcomes for which there is robust or moderate epidemiologic evidence that demonstrates (or indicates) inorganic arsenic causes (or likely causes) human health effects[24] and were prioritized for dose-response analysis.

[24]Lung and bladder cancer are accepted hazard outcomes for iAs based on robust evidence and previous assessments by EPA and other health agencies and similar to four other outcomes EPA continued to prioritize these endpoints for further dose-response analysis.

Table 3-10. Hazard identification evidence judgment summary

Health outcome category	NRC tier	Evidence judgments	Measures considered in different studies
Bladder cancer	**1**	**Accepted hazard**	Bladder cancer mortality All urinary cancer Bladder cancer Urinary transitional cell carcinoma Urothelial carcinoma
Lung cancer	**1**	**Accepted hazard**	Lung cancer mortality Lung adenocarcinoma Lung cancer Other lung cancer histopath types Squamous cell carcinoma
Diabetes	**2**	**Evidence demonstrates**	Diabetes mortality Type 2 diabetes
Diseases of the circulatory system	**1 & 3**	**Evidence demonstrates**	IHD IHD mortality CVD CVD mortality Cerebrovascular disease and stroke Cerebrovascular disease and stroke mortality Hypertension Atherosclerosis Electrocardiogram abnormalities Circulatory markers of cardiovascular disease
Fetal, newborn, and infant health outcomes	**2 & 3**	**Evidence indicates**	Fetal & infant mortality Birthweight Prematurity Fetal growth Postnatal growth
Neurodevelopmental effects	**2**	**Evidence indicates**	Developmental neurocognitive effects Social, behavioral, and emotional effects Motor effects Developmental delays

When the toxicological database is limited to laboratory studies or when there are limited high-quality epidemiology studies available, the RfD and CSF will often be derived from a single POD, generally a BMDL, that is estimated from the best individual study. However, when multiple epidemiological studies of suitable quality are available (i.e., *medium* or *high* confidence), dose-response meta-analyses can increase the precision of the estimated POD (U.S. EPA, 2022) and the POD is more robust given it is based on multiple studies rather than a single study. Given the extensive epidemiologic database for iAs, both noncancer and cancer values could confidently be derived from *high* and *medium* confidence studies. Traditional reference doses were derived for

noncancer endpoints, whereas dose-response slopes were derived from the probabilistic analyses for noncancer and cancer endpoints alike. Both the RfD and dose-response slopes were deemed useful after consulting with EPA Program Offices as they support regulator activities and benefit-cost analyses.

Section 4.3 focuses on dose-response meta-analyses of bladder cancer, lung cancer, diseases of the circulatory system (DCS) and diabetes. These dose-response meta-analyses allowed for estimates of risks above and below the RfD, as well as CSF estimates that are based on more than one POD. Dose-response analyses for fetal, newborn, and infant health outcomes and neurodevelopmental effects are featured Sections 4.4 and 4.5. For several of the outcomes in Table 3-10, epidemiological data exist for exposures below 100 μg/L drinking water or an equivalent dose, and a validated PK model (described in Section 3.1) is available to facilitate improved dose estimation and comparisons among studies. As discussed in the EPA arsenic assessment protocol (Appendix A, page 5-9), the NRC recommended focusing on studies that involved drinking water exposures of 100 μg/L and below. Thus, in Section 4, EPA explores dose-response below 100 μg/L exposures and develops risk estimates across the array of health effects. Note that when exposure levels higher than 100 μg/L were included in studies, these doses were not excluded from dose-response analyses. Then, consistent with the NRC recommendations, risk-specific doses are derived "to address the needs of analyses that would typically use a reference dose (RfD) "… to facilitate efforts to evaluate cumulative risks posed by exposure to multiple chemicals, conduct risk–benefit assessments, or to conduct other comparative analyses" (NRC, 2013).

3.3.1. Mechanistic Observations and Biological Plausibility

Mode of action (MOA) analyses conducted by EPA support the estimated cancer risk results (see Appendix A in the Protocol document (link to protocol)). Briefly, EPA conducted MOA analyses to characterize MOAs associated with arsenic exposure, focusing on MOAs common to multiple adverse health effects versus tissue-specific descriptions. Mechanisms of arsenic-associated disease induction are complex and appear interrelated and are likely involved in both cancer and noncancer disease outcomes. In their analyses EPA focused on seven MOAs: 1) Reactive oxygen species (ROS) generation and oxidative stress responses; 2) As(III) binding to thiol groups and inhibition of key enzymes; 3) As(V) inhibition of oxidative phosphorylation (As[V] structural analog of phosphate); 4) Cell cycling and damage repair impairment; 5) Epigenetics; 6) Endocrine disruption; and 7) Cytotoxicity and regenerative proliferation. Of these, "reactive oxygen species (ROS) generation and oxidative stress responses" has been shown to be a relevant mode of action for multiple arsenic-induced diseases including cardiovascular disease, diabetes, liver disease, lung cancer, bladder cancer, neurotoxicity, nonmalignant respiratory disease, pregnancy outcomes, renal disease, skin cancer, and skin lesions.

Arsenic metabolism in mammals involves cascades of oxidation-reduction (redox) reactions that deplete cellular thiols involved in maintaining cellular redox balance, produce trivalent

methylated species, and the generate ROS. For this reason, it biologically plausible that ROS mediated adverse health effects may result following exposure to inorganic arsenic (Kitchin and Conolly, 2010; Jomova et al., 2011; Flora, 2011). Perturbation of redox balance though ROS generation [e.g., formation of superoxide, H_2O_2, hydroxyl radical) and depletion of antioxidant defenses (e.g., glutathione (GSH) superoxide dismutase) (Kitchin and Conolly, 2010; Jomova et al., 2011; Flora, 2011; De Vizcaya-Ruiz et al., 2009). A variety of oxidative stress markers have been measured in in vitro cell systems in the low μM range, and in animal studies in the low mg/kg-day ranges (0.5–1.7 mg/kg) (see Appendix A, Section A.3, Table A-4 in the Protocol document (link to protocol)).

For each of the cancer and noncancer health outcomes associated with arsenic exposure analyzed in this section: cancer (e.g., lung, bladder), IHD, diabetes, pregnancy outcomes, and developmental neurocognitive, the specific molecular initiating events (MIEs) and subsequent Key Events (KEs) may differ, but they follow a similar general pattern: the generation of ROS, depletion of antioxidant defenses, and perturbation of cellular redox balance. Subsequent KEs in these varied but related MOAs involve changes in protein expression and enzyme activity, lipid oxidation, DNA damage, changes in gene expression and cell signaling. 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]) (Zheng et al., 2012; Zhao et al., 2012; Li et al., 2011) and DNA repair (e.g., DNA polymerase β) (Snow et al., 2005) may occur across multiple cell types, other observations of elevated protein levels may be cell-specific (e.g., platelet endothelial cell adhesion molecule) (Straub et al., 2008).

3.3.2. Cancer

Mechanistic evidence from human in vitro cell models, specifically human urothelial cells, shows that iAs produced ROS may also activate RAS signaling and activation of ErbB2 receptor (Eblin et al., 2007; Eblin et al., 2009), activate growth factor and cytokine activation (Escudero-Lourdes et al., 2012), damages DNA and promotes p53 dysregulation (Wnek et al., 2009; Sun et al., 2014; Kojima et al., 2009; Escudero-Lourdes et al., 2012; Drobna et al., 2003), and perturbs DNA repair enzymes such as OGG1 and p53 (Wnek et al., 2009).

Evidence suggests that persistent inorganic arsenic exposure may result in prolonged activation of the Nrf2 transcription factor pathway (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) (Lau et al., 2013). Data indicate that inorganic arsenic exposure may mimic constitutive Nrf2 activation found in several tumor types (Lau et al., 2013). Like 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-1α 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. These data taken together add to the weight of evidence that it is biologically plausible that inorganic arsenic exposure increases the risk for human bladder and lung cancer.

4. DOSE-RESPONSE ANALYSIS

4.1. INTRODUCTION

For this assessment, EPA evaluated and applied traditional (single-study), meta-analytical, and Bayesian dose-response methods to utilize a wider array of studies more fully in the derivation of toxicity values.

The iAs assessment provides multiple toxicity values for both cancer and noncancer endpoints in order to meet a broad range of stakeholder needs. For noncancer endpoints, the assessment includes the standard derivation of a reference dose (RfD) along with organ- or system-specific RfDs (osRfDs) via the application of uncertainty factors to points-of-departure (PODs). Certain decisions made by EPA Regional and Program Offices rely on the use of RfDs to meet their statutory requirements. Likewise, cancer slope factors (based on the 95th percent upper bound on lifetime risk)[25] are estimated for individual cancer endpoints and a combined cancer oral slope factor (OSF) is estimated based on bladder and lung cancers (Section 4.7). The iAs assessment also includes extensive results of the probabilistic Bayesian dose-response analyses for cancer and noncancer outcomes, where "risk-at-a-dose" values are presented across a range of low- to moderate iAs exposure scenarios. The PODs supporting the RfD are based on the lower confidence limit of the benchmark dose (BMDL) identified from the underlying Bayesian dose-response analyses for ischemic heart disease (IHD) and diabetes (Section 4.6).

Presentation of traditional, noncancer toxicity values (i.e., the RfD and osRfDs) as well as probabilistic toxicity values (i.e., risk-at-a-dose values) will allow users of the iAs assessment to estimate lifetime extra risk for individual endpoints at levels above the final RfD, noting that the definition of the RfD is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." Both the traditional and probabilistic toxicity values are useful within specific decision contexts. However, they involve different assumptions, methods, and uncertainties in their derivation. These results are carefully considered and discussed in this section.

The dose-response methods utilized by EPA were described and reviewed in the iAs protocol (see Appendix A) and are consistent with approaches described in the IRIS Handbook (U.S. EPA, 2022). EPA's approach to the dose-response assessment and toxicity value derivations for iAs in this assessment is directly responsive to advice from NAS on the development of this IRIS

[25] Using the one-sided 95th percent upper bound on risk to derive cancer slope factors is standard practice and is consistent with EPA Cancer Guidelines (U.S. EPA, 2005a).

assessment of iAs specifically (NASEM, 2019), as well as to more generalized NRC recommendations for expanding the use of Bayesian methods and taking a more consistent, unified approach for cancer and noncancer endpoints (NRC, 2009, 2013, 2014; NASEM, 2019). The dose-response methods used in this assessment rely on an estimate of "background" oral iAs intake of 0.365 μg/kg-day (comprising both drinking water and dietary exposure components) in the U.S. population. Population-specific exposure factors that influence the estimation of iAs intake (dose) were used to estimate a common dose measure (average lifetime μg/kg – day) to increase the number of studies that could be combined in the dose-response meta-analysis. The exposure factors came from reported exposure metrics (e.g., water concentrations) and empirical relationships between intake (dose) and reported urinary levels (in units of μg total urinary As/g creatinine), as established by a validated iAs PBPK model[26]. In addition, to take advantage of the large iAs epidemiological evidence base, dose-response meta-analysis methods were used to convert different reported exposure metrics to a common μg/kg-day dose metric (see Section 4.3.2). This common dose metric enabled studies using differing exposure metrics to be combined.

When possible, dose-response meta-analyses, such as those described in (Allen et al., 2020b; Allen et al., 2020a), are used to quantitatively combine results within a set of studies. This includes use of dose-response methods to convert reported incidence data to "effective counts" (see Section 4.3.3), which retains the study-specific control for confounding variables and use of the logistic-power model in order to include case-control and cohort studies in the same meta-analysis. The dose-response meta-analysis modeling approach used enables variability in the dose-response slope estimates to be quantified across study populations. To the extent possible, a variety of sensitivity analyses are performed in this assessment to quantitatively assess model uncertainty, exposure uncertainty, biological considerations, and individual and study population variability.

The endpoint-specific Bayesian dose-response meta-analyses of bladder and lung cancer, ischemic heart disease (IHD),[27] and diabetes were used to derive model-based predictions of mean lifetime extra risk (with confidence intervals) above an exposure level of 0 μg/kg-day, across ranges of oral doses relevant to the U.S. population. In the assessment, these probabilistic risk values are presented in tables and the text as lifetime extra risk per 10,000 persons at various doses at and above the estimated iAs background dose (for cancer endpoints) and above the derived RfD (for

[26]Note that the empirical relationship between urinary total arsenic (tAs) biomarker concentrations and drinking water concentration was established by the El-Masri and Kenyon PBPK model (El-Masri and Kenyon, 2008) and used in all dose conversions of urinary biomarker studies (see Appendix C.1.1 for details and Table C-2 for equations used in conversions. The PBPK model was not run individually for each study.

[27]Studies of ischemic heart disease can include only incident cases, only fatal cases, or can include a mix of both incident and fatal cases. The dose-response analysis of ischemic heart disease *advanced for candidate toxicity value* included incident-only or incident and fatal cases (see Section 4.3.1). However, given the increased severity of fatal vs. nonfatal events, the dose-response analysis for IHD took this into account when defining the benchmark response (see Section 4.61 and Appendix C.1.3), and additional sensitivity analyses and comparisons included in Appendix C.1.2 (Ischemic Heart Disease (IHD) Incidence, Fatal IHD Lifetime Extra Risks).

non-cancer endpoints). Linear and/or polynomial equations are also provided to facilitate the estimation of extra risk at other doses for the modeled endpoints. The selected presentation of extra risk per 10,000 is done for illustration and context and does not represent a "threshold" recommendation, nor is this assessment recommending comparisons (e.g., between cancer and noncancer risk levels). In addition, while it is common practice for certain risk levels (i.e., 1 in a 1,000,000, 1 in 10,000, etc.) to be used by risk assessors when characterizing cancer risk values, this assessment is not suggesting risk levels for potential use in characterizing non-cancer and cancer risks.

The Bayesian dose-response meta-analysis modeling uses a prior distribution for the slope parameter that does not allow negative values. This decision is consistent with the causality conclusions drawn during hazard identification (see Section 4.3.4 for details), since a negative slope would identify decreasing risks for the identified health hazards with increasing iAs exposure. Further, this prior distribution is diffuse, and allows for the probability of both weak and strong associations between iAs exposure and disease, as informed by the modeled data. The hierarchical structure of the Bayesian dose-response meta-analysis model, which estimates separate slope parameters for each individual study data set, provides insight into dose-response heterogeneity and improves the quantification of overall uncertainty and variability.

This dose-response section summarizes (1) the results of an exposure-response screening analysis of epidemiological data sets to help prioritize health outcomes for dose-response (see Section 4.2); (2) Bayesian dose-response meta-analyses for four prioritized health outcomes: bladder cancer, lung cancer, IHD, and diabetes (see Section 4.3); and (3) dose-response analysis for two other prioritized health outcomes with data sets not suitable for Bayesian dose-response meta-analysis: fetal, newborn, and infant health outcomes (see Section 4.4) and neurodevelopmental cognitive effects (see Section 4.5). For cancer endpoints, risk estimates with confidence intervals and cancer slope factors (CSFs) are derived for bladder cancer (see Section 4.3.5) and lung cancer (see Section 4.3.6), and a combined cancer slope factor is derived in Section 4.7. Polynomial equations relating extra risk and dose above background are provided for these cancer types (Sections 4.3.5 and 4.3.6) as well as for IHD (Section 4.3.7) and for diabetes (4.3.8). For IHD; diabetes; fetal, newborn, and infant health outcomes; and neurodevelopmental cognitive effect, separate osRfDs are derived and a single, overall RfD is selected (Section 4.6).

4.2. EXPOSURE-RESPONSE SCREENING FOR ALL OUTCOMES

4.2.1. Overview of Screening Approach

To address the extensive inorganic arsenic evidence base (hundreds of epidemiological studies covering all causal or likely causal health outcomes), an exposure-response screening-level approach was developed (Hobbie et al., 2020) and applied to available dose-response data sets. The primary objectives of the exposure-response screening were to help prioritize health outcomes for dose-response analysis (i.e., identify health outcomes with modeling results close to U.S.

background exposures), identify those that allow for multiple-study dose-response meta-analyses, select the most appropriate data sets for modeling, and provide screening-level relative risk estimates for a broad set of health outcomes potentially useful for cost-benefit considerations. The methods are described by Hobbie et al. (2020). The screening approach was applied to 12 of the health outcomes identified in the NRC "Hierarchy of Health End Points of Concern for Arsenic" (NRC, 2013) for which epidemiological evidence of an arsenic-association was determined robust or moderate[28] (see the iAs Protocol [link provided in Appendix A, Section 2.3.1], Table 5-3). The screening analysis involved deriving and comparing study/data set-specific unitless ratios of the exposure associated with a defined relative risk increase over the background exposure (RRB) (Hobbie et al., 2020). This derivation was completed for all relevant data sets except those for the immune and developmental neurocognitive health outcomes. No appropriate dose-response data sets were identified for immune system health outcomes. The developmental neurocognitive health outcome was analyzed separately because all measured responses are continuous outcomes (e.g., IQ) that cannot be analyzed with this screening approach (Hobbie et al., 2020).

For the iAs exposure-response screening, the RRB estimates were derived by fitting standard parametric exposure-response models (e.g., logistic or Poisson regression) to the exposure metrics provided by study authors and deriving the exposure associated with a 20% increase in relative risk (RRE_{20}). This RRE_{20} value was then divided an exposure estimate of either the population background or the mean background exposure for the study population to generate RRP-US and RRB-SP values, respectively (Hobbie et al., 2020). In addition to the RRB ratio value, another key factor in determining which outcomes to advance for further dose-response analysis was the number of data sets available for a given outcome. Full details of this screening analysis can be found in Appendix A and Hobbie et al. (2020).

Figure 4-1 shows individual and median health outcome-specific RRB-US results organized by highest to lowest number of supporting data sets and nature of the outcome (preclinical/subclinical, clinical nonfatal, or clinical fatal). As can be seen, DCS, bladder cancer, and lung cancer have by far the most extensive evidence base of the screening endpoints, and RRB values for 58, 53, and 28 studies were derived for these endpoints, respectively. Other endpoints that have previously been the focus of iAs assessments, namely skin cancer and skin lesions, had relatively fewer studies appropriate for RRB derivation (7 and 20, respectively). Further, DCS, bladder cancer, and lung cancer generally had lower median RRB-US values than other screened endpoints. These endpoints returned clinical nonfatal RRB-US values of 5.2 (DCS), 7.2 (bladder cancer), and 35.5 (lung cancer). Additionally, DCS and lung cancer had clinical fatal RRB-US values of 8.3 and 4.3. In comparison, skin lesions and skin cancer had generally higher clinical nonfatal

[28]Endpoints with *Robust* strength of evidence: lung cancer, bladder cancer, skin cancer, IHD and CVD, skin lesions, diabetes, stroke; endpoints with *Moderate* evidence: renal cancer, nonmalignant respiratory disease, pregnancy outcomes (infant morbidity and mortality), neurodevelopmental toxicity, immune effects, liver cancer; See Table 5-3 of Protocol for details.

RRB-US values of 42.2 and 18.8, respectively. The results of the RRB analysis, considering both the number of adequate supporting studies and the relatively high percentage of low RRB-US values[29] derived from these studies (Hobbie et al., 2020), support EPA's decision to perform higher-level dose-response analyses for bladder cancer (see Section 4.3.5), lung cancer (see Section 4.3.6), DCS (see Section 4.3.7). The RRB results (i.e., fewer studies available for analysis and/or higher RRB-US values) also support the decision not to perform higher-level dose-response analyses for skin lesions, renal cancer, liver cancer, immune effects, and skin cancer at this time. While initially not identified as a priority endpoint from the screening analysis, diabetes was also selected for higher-level dose-response analysis (see Section 4.3.8) given feedback from EPA's program and regional offices. Although diabetes did have fewer available studies for analysis (n = 8), modeling this endpoint did result in relatively low median clinical nonfatal (3.99) and fatal (5.9) RRB-US values. Higher-level dose-response analyses were also performed for fetal, newborn, and infant health outcomes (see Section 4.4) and developmental neurocognitive effects (see Section 4.5), due primarily to their inclusion of potentially susceptible lifestages and their importance for EPA Program and Regional Office consideration in cost-benefit analyses.

[29]RRB-US estimates are estimated by dividing a study-specific estimate of the exposure level associated with a given relative risk (RRE) by an estimated U.S. background exposure level (in terms of the study-specific exposure metrics); the lower an RRB-US value, the greater the concern. The RRB-US estimates are the focus here as they are more relevant for low exposure populations like the U.S.

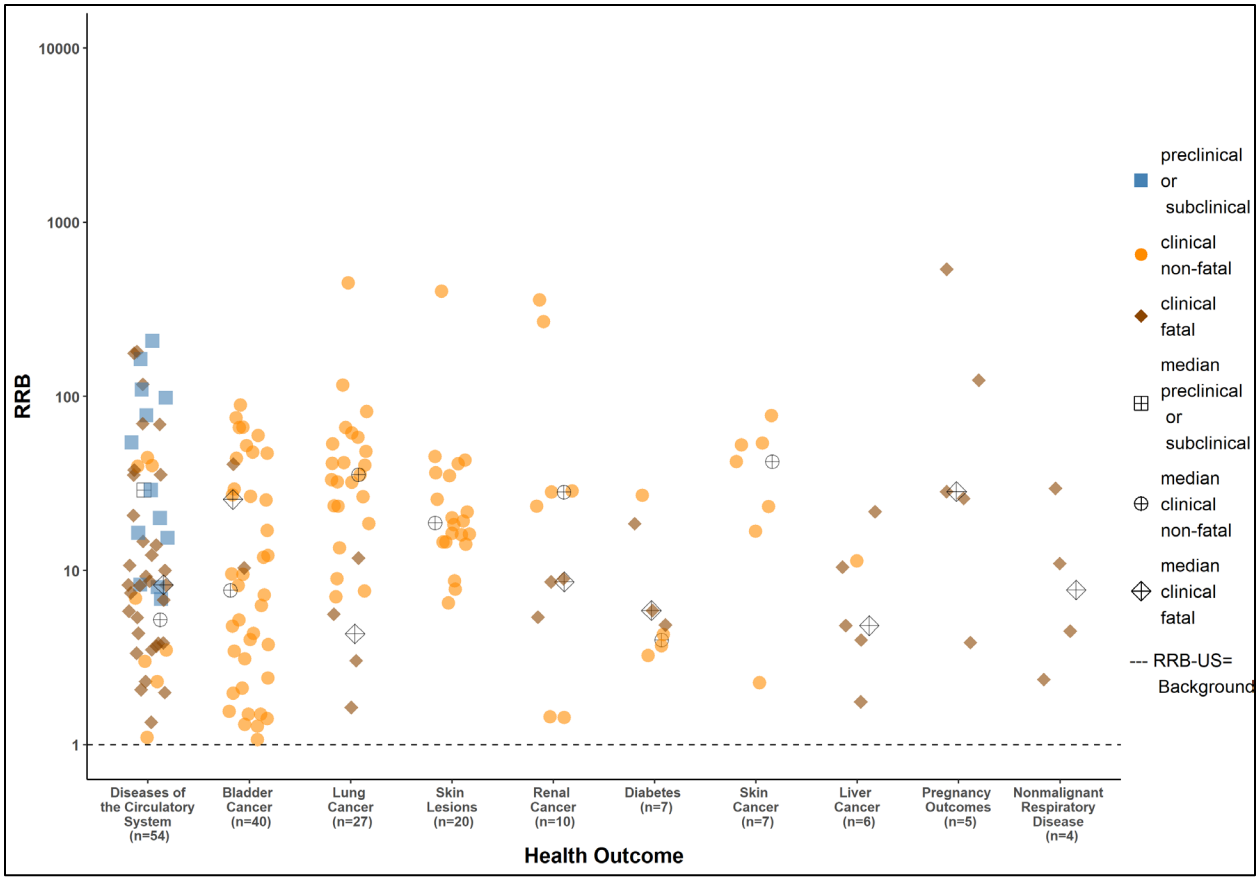


Figure 4-1. Individual data set (solid symbols) and median (crosshatch symbols) relative risk increase over the U.S. background exposure (RRB-US) estimates for modeled health outcomes.[30]

4.3. BAYESIAN DOSE-RESPONSE META-ANALYSES

4.3.1. Identification of Studies and Data for Bladder Cancer, Lung Cancer, Ischemic Heart Disease, and Diabetes Dose-Response Meta-Analyses

The procedures used to select studies and evaluate data sets for inclusion in the Bayesian dose-response meta-analyses for bladder cancer, lung cancer, ischemic heart disease (IHD), and diabetes are described below. These same procedures were used for meta-analysis and/or individual dose-response analyses for fetal, newborn, and infant health outcomes (birth weight) and developmental neurocognitive effects (IQ score) described in Sections 4.4 and 4.5, respectively.

Multiple selection criteria and scientific considerations of particular topics important for EPA's dose-response meta-analysis approach were considered to identify the most appropriate study data sets for use in the dose-response meta-analyses and individual study analyses:

[30]RRB-US values were not derived if the RRE-US$_{20}$ estimate was more than a factor of three below the central estimate for the lowest dose group or above the central estimate for the highest dose group of the study (Hobbie et al., 2020).

1) Selection criteria:

   a) Study design; Case-control or cohort for bladder cancer, lung cancer, IHD, and diabetes. Cross-sectional studies were excluded for all but the fetal, newborn, and infant health and developmental neurocognitive meta-analyses. Ecological studies were excluded from all analyses.

   b) Exposure metrics: Use of exposure metric that is or can be converted to an oral ingestion rate such as drinking water concentrations or creatinine-adjusted urinary concentrations. Studies using other biomarkers (e.g., blood and hair concentrations) were excluded from the dose-response analyses due to uncertainties in converting those metrics to oral doses. For studies conducted in adult populations, the empirical relationship derived using the El-Masri-Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018a, b) allows for the conversion of urine biomarker data (measured in μg tAs/g creatinine) to oral doses, Urine biomarker data based on use of specific gravity as the method for urinary correction were excluded for adult data because that fell outside the application domain of the El-Masri-Kenyon PBPK model. The empirical relationship reported in Moon et al. (2013) allows the conversion of toenail iAs concentrations into drinking water concentrations. For birth weight and developmental neurocognitive effects, maternal urinary total As concentrations were converted to drinking water exposures using the relationship established in Gilbert-Diamond et al., 2016. Specific gravity-corrected urinary biomarker data were considered for birth weight and developmental neurocognitive outcomes given the El-Masri-Kenyon PBPK model was not being used for dose conversions. For birth weight and developmental neurocognitive effects, the toenail studies were excluded because of the uncertainty in applying Moon et al. (2013) to maternal samples.

   c) Smoking: Smoking is associated with both arsenic exposure and the outcomes evaluated in this assessment (Sasco et al., 2004; Salihu and Wilson, 2007; Ockene and NH, 1997; Corrêa et al., 2021; Chen et al., 2013a; ADA, 2004). As such, whether smoking was adequately addressed in the study design and/or analysis was a key criteria for dose-response study selection. If a study did not mention smoking or how the authors addressed confounding due to tobacco smoke exposure and smoking rates in the population were anticipated to be non-negligible, the study was excluded from consideration for dose-response.

   d) Appropriate risk metrics reported: RR, OR, or HR were necessary inputs for the Bayesian dose-response meta-analysis; beta coefficients were the necessary inputs for the birth weight and developmental neurocognitive meta-analyses.

   e) Quantitative exposure reporting: numeric exposure groups characterization was necessary for dichotomous endpoints modeled with the Bayesian dose-response meta-analysis approach whereas study-reported beta coefficients were used for the continuous birth weight and developmental neurocognitive endpoints.

   f) Number of cases, controls, person-years: the numbers of cases, controls, and person-years was a necessary input for the Bayesian dose-response meta-analyses.

   g) Prioritization of endpoints: some health endpoints within a larger domain were prioritized for dose-response modeling. For example, within the larger domain of diseases of the circulatory system, ischemic heart disease was prioritized. Likewise, for fetal, newborn, and infant health outcomes, decreased birth weight was prioritized (see endpoint-specific study

selection sections for more details). Three studies are considered the minimum amount that is sufficient to base a dose-response meta-analysis; outcomes with less than three studies were therefore excluded from further analysis.

2) Other scientific considerations important for dose-response modeling:

   a) To enhance the relevance and precision of the meta-analyses, EPA prioritized including studies for which exposures were low to moderate and well-characterized, recognizing a large proportion of available studies evaluated populations with exposures much higher than commonly experienced in the United States. Thus, this analysis does not include studies of populations within southwest Taiwan, where exposures are not well-characterized, and diseases associated with historically high arsenic exposures have been "endemic" for centuries. Some studies that could be considered moderate to high exposure such as Bangladeshi or Chilean studies were included because they included potentially susceptible subpopulations that received well-characterized[31] exposures for a relatively short period of time: 1958–1970). The inclusion of potentially susceptible subpopulations in the dose-response meta-analysis data sets helps address concerns related to the potential presence of genetic polymorphisms, inadequate nutrition, or other differences that can influence dose-response sensitivity. Selecting diverse studies also facilitates the investigation of heterogeneity in arsenic-related dose-response.

   b) Exclusion of duplicate study populations: Usage of multiple studies from the same population was a consideration in the revised study selection workflow such that duplicate study populations were not used in the same meta-analysis. When multiple studies covered the same study population, only a single representative study was used in the dose-response meta-analysis. For cohort studies conducted using the same cohort population, studies that included a longer follow-up period were generally preferred. However, some cases studies with shorter follow up were selected for inclusion if other characteristics (e.g., more dose groups) favored their use over other studies. When case-control studies drawn from the same study population, only one study was included and studies with longer recruitment periods and greater numbers of cases were preferred. Note that when two case-control studies are conducted in the same *geographic* population, both are included in the dose-response meta-analysis if they fulfill the requirement of nonoverlapping recruitment periods and all other study-selection criteria.

   c) Confirmation of no significant analysis or exposure issues: occasionally, additional study details were considered regarding the suitability of individual studies for inclusion in the dose-response meta-analyses. For example, studies where the exposure range was narrow, and the largest dose group differed by less than 20% of the reference dose were excluded from the dose-response analysis (see study selection for lung cancer). Another example is exclusion of birth weight studies that reported beta coefficients for the z-score for birth weight and not the beta coefficient for the unstandardized birth weight. Datasets that considered the contribution of arsenobetaine (or accounted for seafood consumption) were

[31]The Chile population studied is unique in that, due to limited water sources, almost everyone drinks water from one of the few large public water supplies. Also, 40 years of historical records of iAs concentrations are available for each of these large supplies. So, unlike SW Taiwan, where high exposures came from thousands of small domestic wells with highly variable arsenic concentrations and few historic records, a person's lifetime arsenic exposure in this area of Chile could be estimated with good accuracy simply by knowing the cities or towns in which that person lived.

preferred when available. These confirmatory analysis or exposure issues are discussed in detail in the endpoint-specific sections below. A number of "leave-one-out" sensitivity analyses were also conducted to explore the impact of issues on dose-response results.

d) Model covariates: Because diabetes and/or hypertension could be on the causal pathway between arsenic exposure and IHD outcomes (Moon et al., 2013), models that did not adjust for those outcomes were preferred when selecting estimates for dose-response.

At least two reviewers independently evaluated studies according to the above selection criteria and scientific considerations. Reviewers then discussed judgments and resolved any differences.

Identification of Studies for Bladder Cancer Dose-Response Analysis

Sixty-one *medium* or high confidence studies with exposure- or dose-response data were considered for dose-response, from which 11 studies (11 data sets) were selected for the final bladder cancer dose-response meta-analysis on the basis of criteria outlined above (see Figure 4-2).

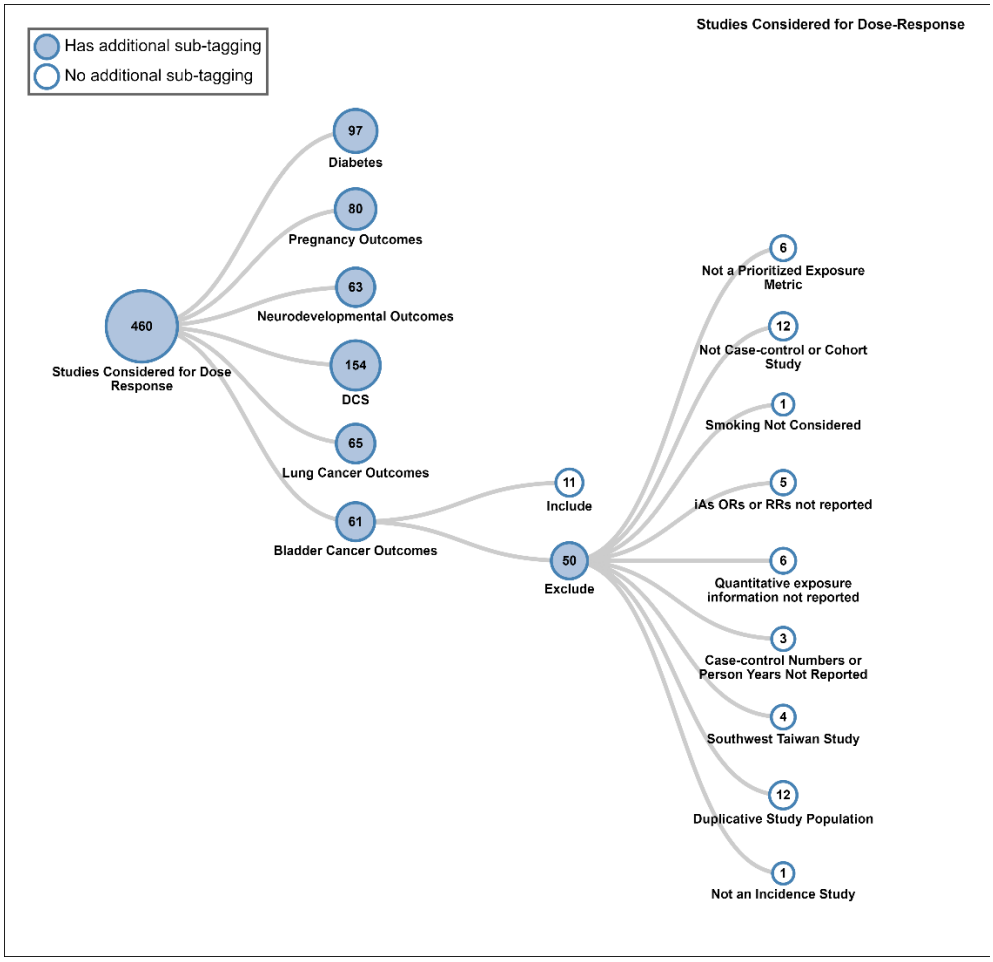


Figure 4-2. Study selection flow for identification of studies for bladder cancer Bayesian dose-response meta-analysis (see interactive version in HAWC).

Data sets selected for urinary/bladder cancer dose-response meta-analysis

Ultimately, 11 studies were included in the dose-response meta-analysis: one cohort study (Chen et al., 2010b), and 10 case-control studies (Wu et al., 2013; Steinmaus et al., 2003; Steinmaus et al., 2013; Michaud et al., 2004; Meliker et al., 2010; Karagas et al., 2004; Chang et al., 2016; Bates et al., 1995; Bates et al., 2004; Baris et al., 2016). Five data sets were from U.S. populations, three from Northeast or Northwest Taiwan, and one each from Argentina, northern Chile, and Finland. See interactive HAWC figure for full list of which studies were excluded under each selection criterion/consideration. The order of appearance of the criteria/consideration in the HAWC figure above reflects the sequence of application (i.e., confirmation of exposure metric was the first screening criteria). Most studies were excluded because they were not cohort or case-control studies, presented duplicative study population data, did not use drinking water, urine, or toenail as the exposure metric, or did not present a RR, OR, or HR as the risk metric. Four studies conducted in SW Taiwan were excluded (Huang et al., 2008a; Hsu et al., 2008; Chiou et al., 1995; Chen et al., 2003). Multiple studies were excluded with respect to the duplicative study population consideration. Steinmaus et al. (2014a), Steinmaus et al. (2015) and Ferreccio et al. (2013) were excluded because these studies investigated the effect of iAs on bladder cancer in population subsets of the main study population (Steinmaus et al., 2013; Chiou et al., 2001a) was an earlier study in the same cohort that was superseded by a later study (Chen et al., 2010b). Yang et al. (2013) was a later study in the same cohort analyses in Chen et al. (2010b), but was not selected for dose-response because it had fewer dose groups than Chen et al. (2010b). Many studies (Wu et al., 2012a; Pu et al., 2007; Lin et al., 2018; Huang et al., 2008b; Huang et al., 2018; Chung et al., 2011a; Chung et al., 2013a) were case-control studies whose recruitment overlapped with Wu et al. (2013). Additionally, one study was excluded because it was a mortality study (studies of bladder cancer incidence was preferred) (D'Ippoliti et al., 2015).

The exposure or intake metrics authors used include lifetime cumulative arsenic intake (from water), daily average intake from water, cumulative exposure (μg/L*years in water), urinary arsenic concentration (μg/g creatinine), and toenail concentration. To support the dose-response meta-analysis, all exposure, intake, and excretion metrics were converted to estimates of lifetime daily arsenic intake. Ranges of estimates for lifetime daily arsenic intake (based on maximum likelihood estimation) and U.S.-equivalent drinking water exposure for each study are also reported in Appendix C.1.2, Table C-25.

Urine biomarker metrics of iAs dose were evaluated against bladder cancer incidence in two hospital-based data sets, consisting of subjects recruited from the National Taiwan University Hospital and the Taipei Municipal Wan Fang Hospital in Northeast Taiwan (Wu et al., 2013) and the China Medical University Hospital located in Midwest Taiwan in the city of Taichung (Chang et al., 2016). EPA estimated daily arsenic intake using the empirical relationship established by the El-Masri-Kenyon PBPK model of the relationships between inorganic arsenic intake and total (inorganic and organic) arsenic urinary excretion (El-Masri and Kenyon, 2008;El-Masri et al.,

2018b;El-Masri et al., 2018a).[32] An important consideration is this Northeast Taiwan study population has been the subject of multiple additional epidemiological investigations (Pu et al., 2007; Huang et al., 2008a; Chung et al., 2011b;Wu et al., 2012a; Chung et al., 2013b; Huang et al., 2018; Lin et al., 2018), all finding similar relationships between bladder cancer and low-level urinary arsenic excretion. This finding corroborates that at least recent exposures from water are consistent with the observed arsenic excretion values.

As noted in Section 1.6.2, ingestion of seafood can result in arsenobetaine contributing to the measured total urinary arsenic concentrations and bias results to the null given that arsenobetaine is a nontoxic species. Therefore, studies using urinary biomarkers to characterize exposure that account for this are preferred as exclusion of nontoxic organic arsenicals may reduce misclassification. Of the two bladder cancer studies using urinary total As to characterize exposure, one (Wu et al., 2013) excluded arsenobetaine in the urinary As concentrations. The other (Chang et al., 2016) stated that it included all organic and inorganic arsenic species in their exposure characterization. The degree to which this study influenced the final modeling results for the dose-response meta-analysis was investigated via the leave-one-out sensitivity analysis discussed in Appendix C.1.2 (Bladder Cancer, Bladder cancer sensitivity analyses). In brief, the sensitivity analysis demonstrated that exclusion of this study did not greatly impact modeling results and only increased the pooled slope parameter by approximately 9% (see Table C-28). EPA found overlap between the studies included in the current dose-response meta-analysis and those identified in six earlier meta-analyses (see Appendix C.1.2, Table C-23). Of the 11 studies chosen by EPA, a core group of five studies were included for all analyses (Meliker et al., 2010; Bates et al., 2004; Baris et al., 2016). Additionally, two studies (Steinmaus et al., 2013; Chen et al., 2010b) were included in five of the six meta-analyses. Many studies selected for the earlier meta-analysis that were not used in the EPA dose-response meta-analysis were studies that were superseded by later analyses of the same study populations or were studies that were judged to be too uncertain regarding exposure measurements (see Appendix C.1.2: Bladder Cancer for more details). In part because of the availability of the El-Masri-Kenyon PBPK model, two recent urine biomarker studies (Wu et al., 2013; Chang et al., 2016) were included in EPA's meta-analysis that were not included in any of the previous meta-analysis. Other studies were not published at the time most of these authors began their literature reviews (Saint-Jacques et al., 2014; Lynch et al., 2017b; Shao et al., 2021).

[32]According to the El-Masri-Kenyon PBPK model, iAs is eliminated almost exclusively in urine. Thus, total μg/kg-day arsenic in urine is a good approximation of μg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. To obtain estimates of μg iAs/kg-day intake, EPA multiplies μg total As/g creatinine (units reported in most studies) by an estimate of g creatinine/kg-day. Urinary creatinine/kg-day is estimated as = $(266.16 - 47.17 \times \text{sex} - 2.33 \times \text{BMI} + 0.66 \times \text{age} + 0.17 \times \text{age}^2) \times 113.12/10^6$, where sex is 0 for male and 1 for female and BMI is estimated as $\text{BW}/(\text{height}/100)^2$. EPA employed a Monte Carlo approach for these derivations to assess the impact of exposure factor variability on the μg iAs/kg-day intake estimates (Allen et al., 2020a).

Identification of Studies for Lung Cancer Dose-Response Analysis

Sixty-five *medium* or *high* confidence studies were considered for dose-response, from which six studies were selected to analyze lung cancer dose-response meta-analysis (see Figure 4-3).

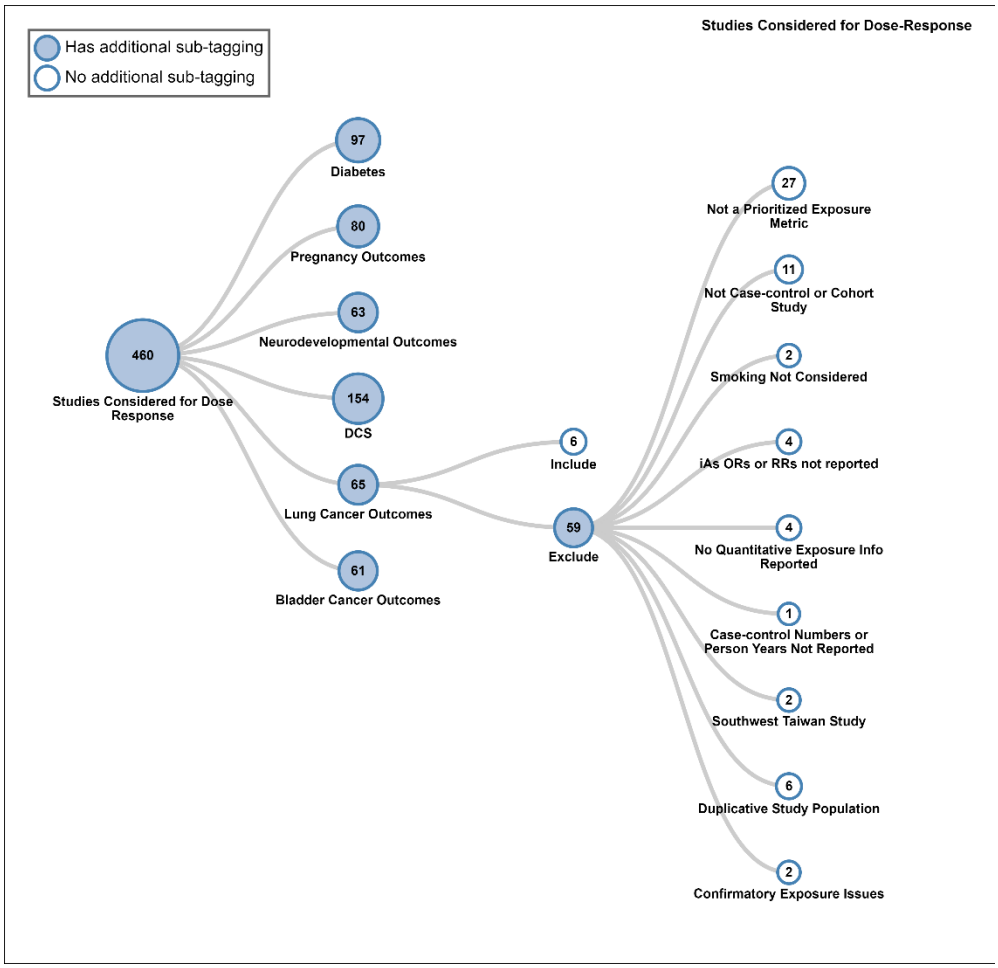


Figure 4-3. Study selection flow for identification of studies for lung cancer Bayesian dose-response meta-analysis (see interactive version in HAWC).

Data sets selected for lung cancer dose-response meta-analysis

Ultimately, six studies were included in the dose-response meta-analysis: three cohort studies (García-Esquinas et al., 2013; Chen et al., 2010a; Argos et al., 2014) and three case-control studies (Steinmaus et al., 2013; Ferreccio et al., 2000; Dauphiné et al., 2013). See interactive HAWC figure for full list of which studies were excluded under each selection criterion/consideration. The order of appearance of the criteria/consideration in the HAWC figure above reflects the sequence of application (i.e., confirmation of exposure metric was the first screening criteria). Most studies were excluded because they did not use drinking water, urine, or toenail concentrations as the exposure metric, were not cohort or case-control studies, or presented duplicative study population

data. Two studies conducted in SW Taiwan were excluded (Chiou et al., 1995; Chen et al., 2004). With respect to duplicative study population data, Steinmaus et al. (2014b), Steinmaus et al. (2014a), Steinmaus et al. (2015) and Ferreccio et al. (2013) investigated the effect of iAs on lung cancer in population subsets of the full study population . Yang et al. (2013) was a later study in the same cohort analyses in Chen et al. (2010a) but was not selected for dose-response because it had fewer dose groups than Chen et al. (2010a). Additionally, two other studies were excluded based on concerns over exposure characterization. Mostafa et al. (2008) characterized exposure based on the mean water concentration for the entire administrative district study participants lived in. Heck et al. (2009) was excluded because, across the entire dose range of the study, exposures only increased by less than 20%.

Appendix C.1.2, Table C-33 lists the six studies selected for inclusion in the Bayesian dose-response meta-analysis for lung cancer. One study was from Northeast Taiwan, one from Bangladesh, and two each from U.S. populations and northern Chile. The exposure or intake metrics authors used include drinking water concentrations, daily average intake from water, cumulative exposure (µg/L*years), urinary arsenic excretion (µg/g creatinine), and toenail concentration (µg/g). Section 4.3.2 describes the approach to addressing exposure measurement uncertainties and estimating arsenic daily intake.

As noted above, EPA estimated daily arsenic intake for two data sets [Argos et al. (2014) and García-Esquinas et al. (2013)], using the empirical relationship between urinary and drinking water concentrations established by the El-Masri and Kenyon PBPK model of the relationships between inorganic arsenic intake and total (inorganic and organic) arsenic urinary excretion (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a).[33] The As intakes estimated in the Argos et al. (2014) study (1.85–18.91 µg/kg-day) are generally in line with those estimated for other selected non-U.S. data sets. Although the estimated daily intakes for García-Esquinas et al. (2013) (0.14–0.58 µg/kg-day) are lower, they are comparable to the other U.S. data set [i.e., Dauphiné et al. (2013): 0.11–2.6], especially at the low end of the exposure range. This makes the García-Esquinas et al. (2013) and Dauphiné et al. (2013) data sets the most sensitive or "critical" studies in the dose-response meta-analysis database. Note that exposure misclassification due to arsenobetaine from seafood ingestion is not a concern for these two studies because the study was either conducted in a population with low seafood consumption or arsenobentaine was measured and observed to contribute a very small (~3%) of the total urinary arsenic concentration.

[33]According to the El-Masri-Kenyon PBPK model, iAs is eliminated almost exclusively in urine. Thus, total µg/kg-day arsenic in urine is a good approximation of µg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. To obtain estimates of µg iAs/kg-day intake, EPA multiplies µg total As/g creatinine (units reported in most studies) by an estimate of g creatinine/kg-day. Urinary creatinine/kg-day is estimated as = $(266.16 - 47.17 \times \text{sex} - 2.33 \times \text{BMI} + 0.66 \times \text{age} + 0.17 \times \text{age}^2) \times 113.12/10^6$, where sex is 0 for male and 1 for female and BMI is estimated as $\text{BW}/(\text{height}/100)^2$. EPA employed a Monte Carlo approach for these derivations to assess the impact of exposure factor variability on the µg iAs/kg-day intake estimates (Allen et al., 2020a).

EPA found considerable overlap between the studies included in the EPA dose-response meta-analysis and those identified in earlier meta-analysis (see Appendix C.1.2, Table C-34). Of the six studies chosen by EPA, only one study (Chen et al., 2010a) was used in all earlier meta-analyses. Two other studies used in the EPA meta-analysis (Dauphiné et al., 2013; Steinmaus et al., 2013) were included in all but one earlier meta-analyses. a core group of five studies were chosen for all; or for all but one (Mostafa et al., 2008; D'Ippoliti et al., 2015) of the meta-analyses published after the eight studies identified by EPA. The four studies selected for the earlier meta-analyses not used in the current dose-response meta-analysis were determined unsuitable because they were conducted in the southwest Taiwan "endemic" region (Chiou et al., 1995; Chen et al., 2004), were re-analyses that used much wider exposure ranges in the low-dose region compared with the original study (Ferreccio et al., 2000), had an unsuitably narrow exposure range (i.e., less than 20% increase in exposure across entire exposure range) (Heck et al., 2009), or were superseded by a later study using the same cohort (Chen et al., 2004).

Identification of Outcomes and Studies for IHD Dose-Response Analysis

Diseases of the circulatory system (DCS)[34] is a broad term used in this assessment to encompass ischemic heart disease (IHD),[35] stroke, high blood pressure, and peripheral artery disease. As discussed in Section 3.2.1, these DCS outcomes have all been linked to iAs exposure. Studies of clinically diagnosed IHD alone, however, have reported dose-response relationships with iAs that generally are stronger than the dose-response relationships for other DCS outcomes, including hypertension and stroke (Moon et al., 2017b). Moreover, NRC (2013) identified IHD as the highest priority DCS outcome for EPA's iAs assessment. For these reasons, the Bayesian dose-response meta-analyses for dose-response described in this section focuses on studies that involve clinical diagnoses of two DCS outcome categories: IHD incidence and IHD fatality.

One hundred and fifty-four *medium* or *high* confidence studies were considered for dose-response, from which seven studies (eight data sets) were selected for the final IHD dose-response meta-analysis (see Figure 4-4).

[34]This terminology is consistent with the latest International Classification of Disease-10 (https://icd.who.int/browse10/2016/en#/).

[35]Another term used in epidemiological studies, coronary heart disease (CHD), is largely synonymous with IHD, but has no specific ICD code; studies that use the term CHD to define cases are included in the IHD sections of this assessment.

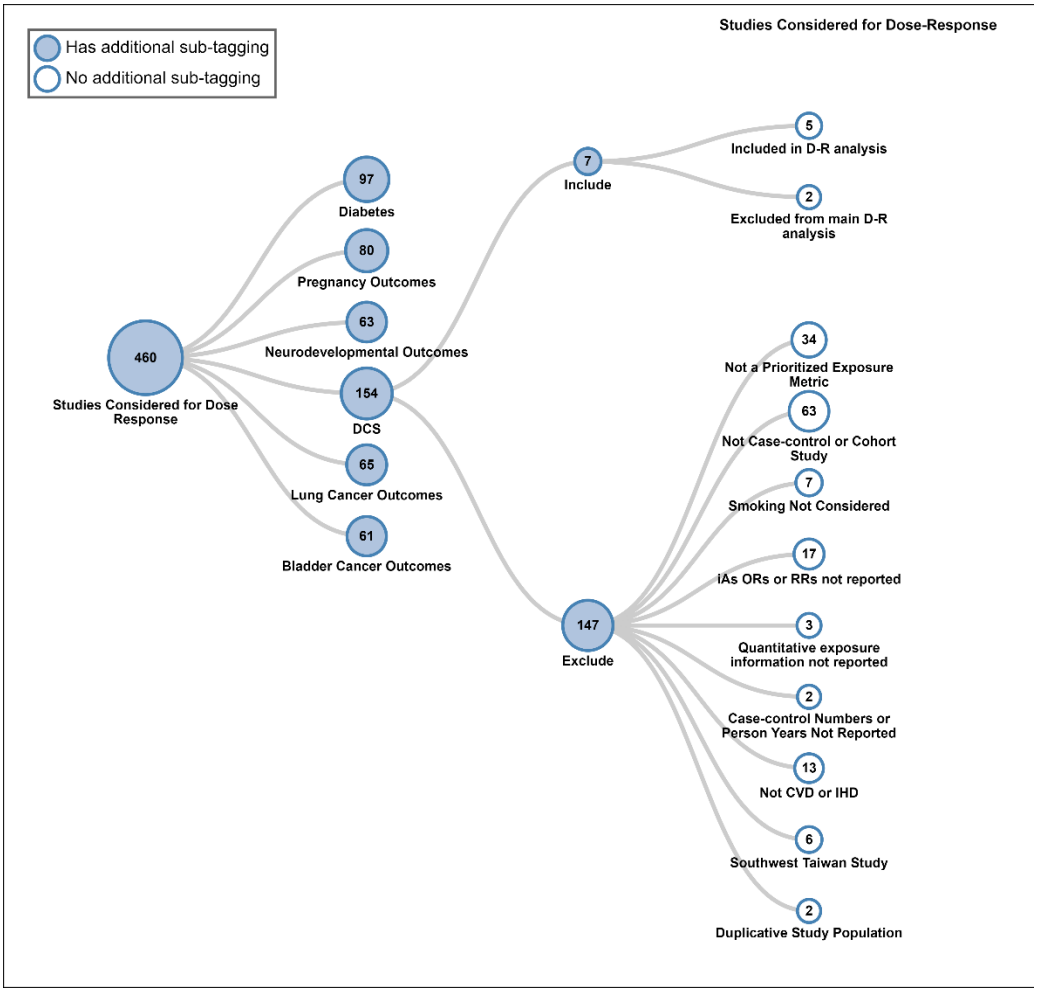


Figure 4-4. Study selection flow for identification of studies for DCS Bayesian dose-response meta-analysis (see interactive version in HAWC).

Data sets selected for IHD dose-response meta-analyses

Ultimately, seven studies were initially identified for inclusion in the dose-response meta-analysis: six cohort studies (Wu et al., 2010b; Nigra et al., 2021; Moon et al., 2013; James et al., 2015; Chen et al., 2011b; Chen et al., 2013c), and one case-control study (Wade et al., 2015). Of these studies, three studies presented information on IHD mortality. However, one IHD mortality study adjusted for urinary dilution via specific gravity (Nigra et al., 2021) and the El-Masri–Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a) was not able to estimate drinking water concentrations for this study (as the empirical relationship established by the PBPK model is between drinking water concentrations and creatinine-adjusted urinary As concentrations). This left only two remaining IHD mortality-only studies (Moon et al., 2013; Chen et al., 2011b), considered too few to form the basis of a dose-response meta-analysis. Thus, only the five remaining IHD studies that included incident-only cases or incident plus fatal cases were ultimately modeled.

See interactive HAWC figure for full list of which studies were excluded under each selection criterion/consideration. The order of appearance of the criteria/consideration in the HAWC figure above reflects the sequence of application (i.e., confirmation of exposure metric was the first screening criteria). Most studies were excluded because they were not cohort or case-control studies, did not use drinking water, urine, or toenail as the exposure metric, did not present a RR, OR, or HR as the risk metric, or did not present information on the prioritized outcomes of CVD or IHD. Six studies conducted in SW Taiwan were excluded (Wang et al., 2002; Tseng et al., 2003; Hsueh et al., 1998; Hsieh et al., 2008b; Chiou et al., 2001b; Chen et al., 1996). Two studies (Wu et al., 2006; Wang et al., 2007) were excluded as duplicate populations of the Wu et al. (2010b) study. Appendix C.1.2, Table C-50 summarizes the five studies, four cohort studies and one case-control study selected for inclusion in the Bayesian dose-response meta-analyses of IHD after dose-response study quality considerations. All the cohort studies were deemed to have involved adequate follow-up durations for IHD health outcomes to occur.[36] The third column of Table C-50 indicates the exposure or intake metrics authors reported; these include daily average intake from water (μg/L) and cumulative exposure (μg/L*years in water) and urinary arsenic excretion (μg/g creatinine). To support the dose-response meta-analysis, all exposure, intake, and excretion metrics were converted to estimates of lifetime daily arsenic intake.

For the Moon et al. (2013) and James et al. (2015) studies, all daily dose and equivalent U.S. drinking water level estimates for the exposure groups are in the range of U.S. doses (<1 μg/kg-day) and U.S. drinking water levels (<100 μg/L). Thus, the results from the Moon et al. (2013) and James et al. (2015) arsenic studies are considered most relevant for assessing the relationship between the relatively low levels of arsenic daily intake most U.S. populations experience and IHD outcomes. Note that exposure misclassification due to arsenobetaine from seafood ingestion was a concern for one urinary biomarker study for IHD (Chen et al., 2013c) because the study did not report that it was conducted in a population in which arsenobentaine was measured or report that arsenobetaine was observed to contribute a very small percentage of the total urinary arsenic concentration. The degree to which this study influenced the final modeling results for the dose-response meta-analysis was investigated via the leave-one-out sensitivity analysis discussed in Appendix C.1.2 (IHD sensitivity analyses). In brief, the sensitivity analysis demonstrated that exclusion of this study had a moderate impact on modeling results, increasing the pooled slope parameter by approximately 30% (see Table C-57).

There was some overlap between the studies included in the EPA dose-response meta-analysis and those identified in earlier meta-analysis (see Appendix C.1.2, Table C-51). A recent meta-analysis, Moon et al. (2017b), that succeeds a previous meta-analysis by the same group (Moon et al., 2012) was identified. The IHD studies selected by Moon et al. (2017b), but excluded

[36]The cohort study follow-up durations ranged from ~6 to 40 years. The low end of this range is not deemed a major concern given the short latency period for iAs-induced DCS relative to iAs-induced cancer (Yuan et al., 2007).

from the EPA dose-response meta-analysis are Rahman et al. (2014), Sohel et al. (2009), Wang et al. (2005), Wade et al. (2009), Farzan et al. (2015a), D'Ippoliti et al. (2015), and Chen et al. (1996). Farzan et al. (2015a) was not included due lack of exposure group quantitative results (i.e., analyses treated arsenic as a continuous variable), Chen et al. (1996) is a study of townships in southwest Taiwan with endemic arseniasis that has experienced very high iAs exposures not relevant to U.S. populations, Wade et al. (2009) reported incident rate ratios instead of relative risks, and D'Ippoliti et al. (2015) did not control for smoking on the individual level, Sohel et al. (2009) did not control for smoking, and Rahman et al. (2014) and Wang et al. (2005) did not investigate IHD endpoints.

Identification of Outcomes and Studies for Diabetes Dose-Response Analysis

Ninety-seven *medium* or *high* confidence studies were considered for dose-response, from which four studies were selected for the final diabetes dose-response meta-analysis (see Figure 4-5).

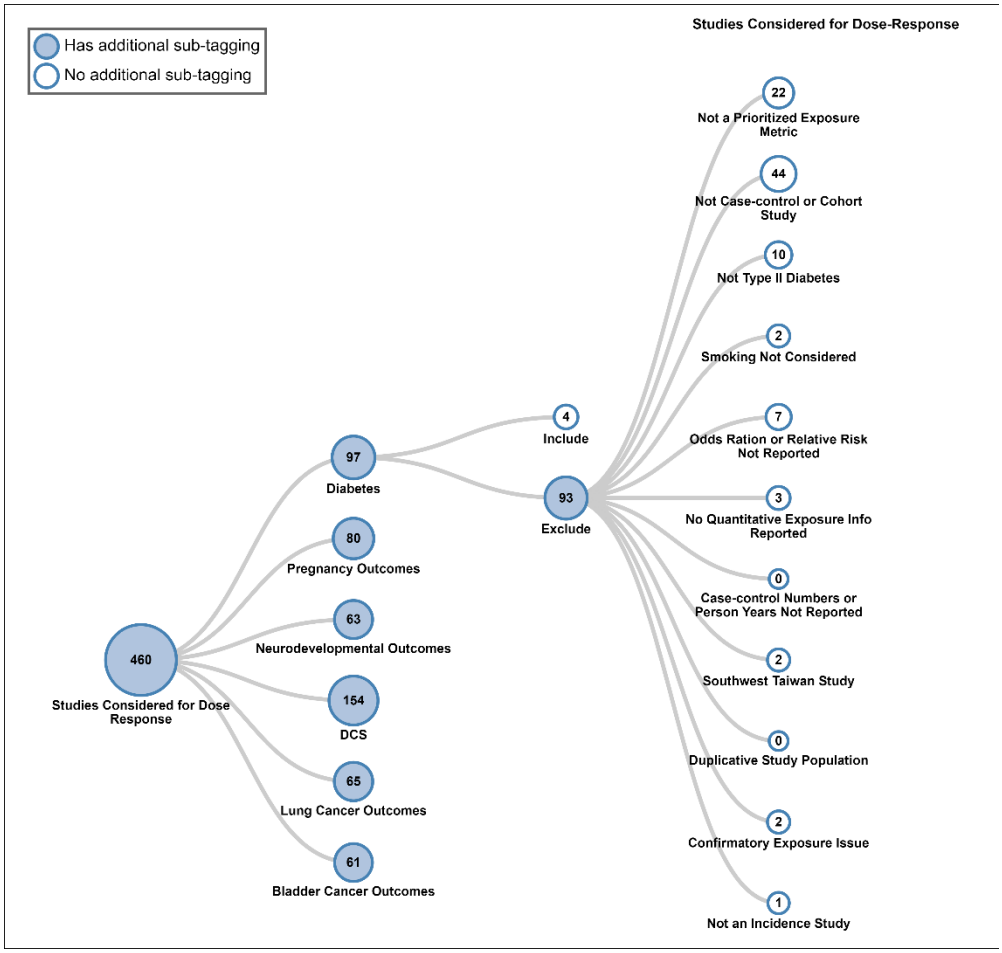


Figure 4-5. Study selection flow for identification of studies for diabetes Bayesian dose-response meta-analysis (see interactive version in HAWC).

Data sets selected for diabetes dose-response meta-analysis

Ultimately, four studies were included in the dose-response meta-analysis: three cohort studies (Pan et al., 2013b; James et al., 2013; Grau-Perez et al., 2017), and one case-control study (Coronado-González et al., 2007). See interactive HAWC figure for full list of which studies were excluded under each selection criterion/consideration. The order of appearance of the criteria/consideration in the HAWC figure above reflects the sequence of application (i.e., confirmation of exposure metric was the first screening criteria). The most common reasons were not using drinking water or urine as the exposure metric, not being a cohort or case-control study, or not being a study of type 2 diabetes incidence, i.e., a study of diabetes mortality was not included (D'Ippoliti et al., 2015). Other exposure considerations that led to exclusion were studies being conducted in southwest Taiwan (Tseng et al., 2000; Hsu et al., 2013), reporting of exposure on the log scale (Rangel-Moreno et al., 2022), or very low doses determined by geographic analysis (Bräuner et al., 2014).

Appendix C.1.2, Table C-42 lists the four data sets selected for inclusion in the Bayesian dose-response meta-analysis for diabetes. One data set was from Bangladesh, one was from Mexico, and two were from the United States. The exposure or intake metrics the authors used include lifetime cumulative arsenic intake (from water), drinking water concentration, and urinary arsenic excretion (μg/g creatinine). To support the dose-response meta-analysis, all exposure, intake, and excretion metrics were converted to estimates of lifetime daily arsenic intake.

As noted above, EPA estimated daily arsenic intake for two data sets (Coronado-González et al., 2007; Grau-Perez et al., 2017), on the basis of the empirical relationship between urinary and drinking water concentrations established by the El-Masri–Kenyon PBPK model of the relationships between inorganic arsenic intake and total (inorganic and organic) arsenic urinary excretion (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a).[37] . The estimated daily iAs intakes for Coronado-González et al. (2007) (1.3–4.56 μg/kg-day) is generally in line with the estimated daily intakes for other selected non-U.S. data sets. The estimated daily intake for Grau-Perez et al. (2017) (0.07–0.28 μg/kg-day), however, is lower than those data sets and is more comparable to the other U.S. data sets used for other endpoints [e.g., the lung cancer Dauphiné et al. (2013) study: 0.11–2.6 μg/kg-day]. The James et al. (2013) cumulative exposure study is also associated with relatively low iAs daily intake values: 0.135–0.608 μg/kg-day. This makes the Grau-Perez et al. (2017) and James et al. (2013) studies the studies that represent the lowest exposure ranges in the dose-response meta-analysis database for type 2 diabetes. Note that exposure

[37]According to the El-Masri-Kenyon PBPK model, iAs is eliminated almost exclusively in urine. Thus, total μg/kg-day arsenic in urine is a good approximation of μg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. To obtain estimates of μg iAs/kg-day intake, EPA multiplies μg total As/g creatinine (units reported in most studies) by an estimate of g creatinine/kg-day. Urinary creatinine/kg-day is estimated as = $(266.16 - 47.17 \times \text{sex} - 2.33 \times \text{BMI} + 0.66 \times \text{age} + 0.17 \times \text{age}^2) \times 113.12/10^6$, where sex is 0 for male and 1 for female and BMI is estimated as $\text{BW}/(\text{height}/100)^2$. EPA employed a Monte Carlo approach for these derivations to assess the impact of exposure factor variability on the μg iAs/kg-day intake estimates (Allen et al., 2020a).

misclassification due to arsenobetaine from seafood ingestion is not a concern for the two urinary biomarker studies because the study was either conducted in a population with low seafood consumption (Coronado-González et al., 2007) or arsenobentaine was not included in the estimation of total urinary arsenic concentrations and sensitivity analyses investigating including arsenobetaine as a confounder in models showed no difference to the main analyses (Grau-Perez et al., 2017).

Wang et al. (2014) performed the only meta-analyses comparable to the EPA dose-response meta-analysis approach in that it involved dose-response meta-analysis modeling of multiple studies of the relation between type 2 diabetes and inorganic arsenic exposure. It differed from the EPA analysis in that it included cross-sectional studies and studies conducted of the iAs endemic region of SW Taiwan region. Of the four diabetes studies used in the EPA analysis, two were included in the Wang et al. (2014) analysis, James et al. (2013) and Coronado-González et al. (2007), but the two later publications, Pan et al. (2013b) and Grau-Perez et al. (2017), were not.

4.3.2. Estimating a Common Dose Metric and Dose Uncertainty for Bladder Cancer, Lung Cancer, Diseases of the Circulatory System, and Diabetes Dose-Response Meta-Analyses

The conversion of study-specific exposure metrics to a common dose metric is an essential aspect of the dose-response meta-analysis approach used by EPA as it allows multiple studies to be combined, which increases the precision of the dose-response modeling results. Allen et al. (2020a) describes methods for performing these dose conversions, and they are also summarized in the updated iAs Protocol, Section 5.2 (see Appendix A) and Appendix C.1.1. Additional details on the methods for treating dose uncertainty are provided in Appendix C.1.1 (Treatment of Dose Uncertainty). Of particular note is that by calculating a common dose metric, the present analysis can include studies that used urinary or toenail biomonitoring as the exposure assessment method and studies that assessed exposure on the basis of drinking water intake. Applications of the empirical relationship between urinary tAs concentrations and drinking water concentrations, as established by the El-Masri–Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a) or the relationship between toenail As concentration and drinking water exposure (Moon et al., 2013) are considered to provide reliable estimates of total arsenic dose and average lifetime daily intake (μg/kg-day) (Allen et al., 2020a; Allen et al., 2020b). Urinary and toenail arsenic measurements integrate all sources of oral exposure at the individual level, accounting for arsenic from both water and diet, an important recommendation of NRC, (2013), and are considered a high-quality biomarker of internal dose (NRC, 1999; Hughes, 2006; Marchiset-Ferlay et al., 2012).

Dose uncertainty was addressed using the two-step approach described by Allen et al. (2020a) and in Appendix C.1.1 (Treatment of Dose Uncertainty). This two-step approach involved deriving estimates for the low, maximum likelihood estimate (MLE), and high exposure-group

means.[38] These estimates then were used in a Monte Carlo analysis, along with distributional representations of individual variability of exposure-to-intake conversion factors, to estimate low (5th percentile), MLE, and high (95th percentile) average μg/kg-day intake doses (Allen et al., 2020a). Appendix C.1.2 provides the three selected sets of dose values (in average μg iAs/kg-day) used in the analyses of bladder cancer, lung cancer, diabetes, and IHD. Appendix C.1.1 (Treatment of Dose Uncertainty) provides details of the study-specific conversions.

4.3.3. Estimating Effective Counts for Bladder Cancer, Lung Cancer, Diseases of the Circulatory System, and Diabetes Dose-Response Meta-Analyses

To further expand the number of studies that could be included in the iAs dose-response meta-analysis approach, data adjustments were also made to the response measures (counts of affected and nonaffected individuals) reported in the studies considered for use. These data adjustments result in "effective counts"—noninteger incidence data that consider the controls for confounding that the individual study authors performed, which allows for case-control and cohort studies to be included in the same dose-response meta-analysis. Essentially, effective counts produce the adjusted OR or RR the study authors report after controlling for confounders. The methods and rationale for deriving effective counts for such study types, described by Allen et al. (2020a) and in Appendix C.1.1 (Adjusting for Covariates), were applied to the bladder cancer, lung cancer, IHD, and diabetes data sets. The resulting effective counts for these four data sets are presented in endpoint-specific subsections of Appendix C.1.2.

4.3.4. Methods Used to Conduct Dose-Response Meta-Analysis and Estimate U.S. Lifetime Extra Risk for Bladder Cancer, Lung Cancer, Diseases of the Circulatory System, and Diabetes

The dose-response meta-analyses for bladder cancer, lung cancer, IHD and diabetes were conducted using Bayesian-derived methods. A logistic-power model was used because it allows for a unified, consistent analysis of both case-control and cohort studies together in a single dose-response meta-analysis (Allen et al., 2020a; Allen et al., 2020b). The basic equation relating dose to response is

$$logit\{Pr(D = 1 \mid X)\} = \alpha^* + \beta^T s(X^q) \quad (4\text{-}1)$$

where $Pr(D = 1 \mid X)$ is the probability of having the disease (D = 1 as opposed to D = 0), which is conditional on the values of the explanatory variables, X, having p components X_1, …, X_p. Here, s(x) is a specified, fixed function and $s(x) = (s_1(x_1), \ldots, s_p(x_p))$. The motivations and methods for

[38]As described in Allen et al. (2020a) low and high estimates were obtained by minimizing and maximizing the high-exposure group means, respectively, subject to the constraint that −2*(LL – MLL) < 2.706 (a 95% bound on the high-group mean). LL is the log-likelihood for the log-normal distribution for the candidate parameter vector; MLL is the maximum log-likelihood. When a published study reports the mean or median values for each group, those values are used directly as the group-specific dose values, with no log-normal fitting.

implementing such an analysis are described by Allen et al. (2020b) and in Appendix C.1.1 (Bayesian Dose-Response Meta-Analysis Methods). X is scalar (having the value of iAs dose in μg/kg-day) and s(x) = x, so β (i.e., the slope) is also a scalar. The q parameter is the exponent on the explanatory dose variable x.

The hierarchical structure for the dose-response meta-analysis assumes the α* parameter was separate and independent for each data set (Allen et al., 2020b). Study-specific β values that were normally distributed around a mean (β_mean) with some standard deviation (β_sigma) were assumed. Both β_mean and β_sigma are estimated from the study-specific values. The parameter β_mean, in particular, is the parameter representing the "pooled" or "average" coefficient for arsenic dose that is a critical parameter in the extrapolation stage, where target-population risks are estimated. Additionally, the estimated power parameter (on the dose term) is not hierarchical, and the estimated value applied to both study-specific and pooled analyses. Prior probability distributions were assigned to the model parameters as shown in Table 4-1.

Table 4-1. Prior parameter values for dose-response meta-analyses

Parameter	Prior distribution
$\beta(i)a$	$Normal\ (\beta\_mean, \beta\_sigma)$
β_mean	$Gamma\ (a\ =\ 0.52, b\ =\ 1.12)$
β_sigma	$Half-Cauchy\ (scale\ =\ 5, location = 0)$
$power\ (q)$	$Half-\ Cauchy\ (scale\ =\ 0.315, location\ =\ 1)$

[a]β(i) is the dose coefficient for data set i.

The gamma prior for β_mean reflects the determination that arsenic is causal for the health outcomes analyzed so that its coefficient in the model should not be negative. A sensitivity analysis using a more complex double Hill model that allows for negative response estimates was conducted to verify the reasonableness of this assumption (see Appendix C.1.1 [Sensitivity Analysis of Possible Nonmonotonic Dose-Response Relationships]). The specific choices for the values of the "a" and "b" parameters that define a gamma distribution are discussed in Allen et al. (2020b) and reflect the judgment that a relatively wide, uninformative prior (see below) should be used for the Bayesian modeling to represent the prior probability of both weak and strong associations between arsenic exposure and bladder cancer incidence. To represent this diffuse prior, a gamma distribution was selected such that the OR would be unlikely to be greater than 20 at a dose of 1 μg/kg-day (p < 0.01) and equally unlikely to be less than 1.0001 at that dose.[39] Sensitivity analyses of this prior choice were conducted and show that alternative priors had no significant impact on the final results for any health outcome (see endpoint-specific subsections of Appendix C.1.2). The prior for the power parameter (q) restricts values for the parameter to obviate supra-linearity. Although the

[39]1 μg/kg – day is 27 times greater than the estimated U.S. background (median) iAs dose of 0.0365 μg/kg – day.

prior does place greatest prior probability for a power value of 1, the 95th percentile for the prior is 18, a very large value for the power that would almost completely flatten out the dose-response curve for low doses (i.e., make the logistic-power model essentially a threshold model). A prior for $\alpha^*(i)$ is not needed; it is a function of $\beta(i)$ and either the expected number in the referent group (for a cohort study) or the proportions of controls in the exposure groups (for a case-control study). Appendix C.1.1 (Bayesian Dose-Response Meta-Analysis Methods), defines those relationships and specifies the priors for those other parameters.

The key output of the dose-response meta-analyses—the posterior distribution for the "pooled" (average) value of the logistic slope and the power parameter—is used in lifetable calculations to estimate the U.S. population lifetime[40] probability of observing a health outcome as a function of iAs dose (average μg/kg-day). The overall methodology is described by Allen et al. (2020a) and Allen et al. (2020b).[41] Details of the lifetable calculations vary by health outcome and are discussed separately in the individual health outcome sections (see Sections 4.3.5 through 4.3.8). An important aspect of all the lifetable applications, however, is that the exposure scenario used posits a continuous, full lifetime exposure to a constant iAs dose, which includes a background U.S. iAs dose that is associated with the background U.S. risks estimated by the lifetables.

For each health outcome analyzed in Sections 4.3.5 through 4.3.8, the focus is on describing the relationship between U.S. lifetime extra risk above an estimate of the U.S. risk at a zero iAs dose and a full lifetime exposure to a constant iAs dose. Estimates for U.S. lifetime background probability of disease of 1.9% for bladder cancer and 5.7% for lung cancer were obtained from CDC lifetables. U.S. lifetime probability of disease of 40% for IHD (Lloyd-Jones et al., 1999),[42] and 40% for diabetes (Gregg et al., 2014)[43] were approximated from published rates due to the lack of lifetable data. The zero-dose U.S. lifetime risks were obtained by extrapolation, using the logistic slope and power estimates obtained from the dose-response meta-analysis and assuming that the U.S. lifetime background risks are associated with a background dose of 0.0365 μg iAs/kg-day (0.02 μg iAs/kg-day from dietary food consumption and 0.0165 μg iAs/kg-day from drinking water).[44] This estimate of background dose is based on median estimates of intake for all ages and is not specific to any particular lifestage. The El-Masri-Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a) indicates this level of U.S. background intake is

[40]For computational purposes, 85 years was used to define the upper limit for lifetime risk calculations.
[41]The lifetable methodology described in Allen et al. (2020b) used the logistic model but is still relevant to the assessment's use of the logistic-power model. Essentially, when using the logistic-power model, the lifetable methodology uses the iteration-specific values for the logistic slope and power parameters in the calculation of lifetime extra risk, instead of just the logistic slope when using the logistic model.
[42] Lloyd-Jones et al. (1999) reported lifetime risks of IHD (CHD) at an index age of 40 years for men (48.6%) and women (31.7%) enrolled in the Framingham Heart Study.
[43] Gregg et al. (2014) reported life risks of diabetes from age 20 for men (40.2%) and women (39.6%) in a large (N = 598, 216) study of National Health Interview Survey participants.
[44]Median U.S. dietary consumption (Xue et al., 2010) plus median U.S. County average inorganic arsenic drinking water concentration (1.5 μg/L) from USGS data (Mendez et al., 2017) multiplied by the average water intake in the U.S. population of 0.011 L/kg-day (U.S. EPA, 2019), Table 3-1, "All Ages").

consistent with the estimated 1–5 μg/L urinary background levels of total arsenic (summing inorganic, monomethyl, and dimethyl arsenic forms) that NRC (2013) considered to a reasonable for the U.S. population.

4.3.5. Bayesian Dose-Response Meta-Analysis Dose-Response Results for Bladder Cancer

Bayesian dose-response analyses for bladder cancer were conducted as previously described (see Sections 4.3.1 to 4.3.4, and Appendix C.1.1). As discussed in Section 4.3.2, dose-response meta-analyses were performed with estimates of low, maximum likelihood, and high doses to investigate dose conversion uncertainties. This section presents the results for dose-response meta-analyses using the MLE doses. The dose-response meta-analyses for bladder cancer included both case-control and cohort studies; the selected 11 studies, converted doses (low, MLE, high) and effective counts used in the bladder cancer dose-response meta-analyses are presented in Appendix C.1.2 (Bladder Cancer). See U.S. EPA (2025) for access to all dose-response input and output files for bladder cancer. U.S. EPA (2024b) provides a structured workflow and variable dictionary for the dose-response files.

A summary of the results of the bladder cancer dose-response meta-analyses using the MLE doses are presented in Table 4-2. The posterior mean for β_sigma is an estimate of the standard deviation of the study-specific β parameter estimates around the estimated mean, β_mean, and is therefore a measure of study-to-study heterogeneity with respect to that key parameter. The posterior mean for β_sigma is 1.35, and its 5th percentile is 0.76 (see Table 4-2). The mean coefficient of variation (CV), β_sigma/β_mean, is 3.7, indicating relatively high heterogeneity. This level of diversity across study slopes justifies the decision to model the slope parameters hierarchically (i.e., a study-specific, separate slope is derived for each study as opposed to estimating a single, common slope for all data sets). Appendix C.1.2 (Bladder Cancer; Summary of Bladder Cancer Dose-Response Meta-Analysis Results for MLE Dose Estimates) contains details of the modeling results, including posterior distribution plots for pooled and data-set-specific logistic slope parameters and nonhierarchical and hierarchical model plots for individual bladder cancer studies and sensitivity analyses (see Appendix C.1.2 Bladder Cancer Sensitivity Analyses).

Table 4-2. Summary of bladder cancer Bayesian analysis output, focusing on parameters important for risk estimation in the target population using MLE doses[a]

Parameter	Mean	Standard deviation	5%	95%
β_mean	0.3694	0.3393	0.0041	1.0253
β_sigma	1.3449	0.4828	0.7551	2.2474
β (Chen et al., 2010c)	0.0807	0.2931	0.0362	0.1266
β (Steinmaus et al., 2013)	0.4548	0.2956	0.2603	0.6572
β (Wu et al., 2013)	2.9557	0.6416	2.1603	3.7522
β (Bates et al., 1995)	0.4321	0.9917	−1.8672	2.7721
β (Steinmaus et al., 2003)	−0.3131	0.8192	−2.2484	1.4424
β (Bates et al., 2004)	−0.1572	0.3238	−0.2956	−0.0376
β (Meliker et al., 2010)	0.1587	0.5518	−0.8982	1.1941
β (Baris et al., 2016)	0.9940	0.5744	−0.0844	2.1180
β (Chang et al., 2016)	0.0956	0.2930	0.0242	0.1735
β (Karagas et al., 2004)	0.3369	0.9837	−1.9864	2.6350
β (Michaud et al., 2004)	0.5248	0.9568	−1.6565	2.7972
power	1.0890	0.0863	1.0050	1.2572

[a]Inference for Stan model: 4 chains, each with iter = 50,000; warmup = 37,500; thin = 1; post-warmup draws per chain = 12,500, total post-warmup draws = 50,000.

Extrapolation of Bladder Cancer Risk to Target Population

β_mean [the posterior distribution for the "pooled" (average) value of the logistic slope parameter] and power were used with U.S. all-cause mortality and bladder cancer incidence rates as input to a lifetable calculation of the lifetime probability of bladder cancer as a function of iAs dose (average μg/kg-day). Allen et al. (2020a) and Allen et al. (2020b) describe the methodology (along with Appendix C.1.1). The exposure scenario used for these extrapolations posits a continuous, full lifetime exposure to a constant iAs dose (including the U.S. background dose).

Age-specific U.S. background lifetable rates used in the analysis are provided in Appendix C.1.2 (Extrapolation of Bladder Cancer Extra Risk to Target U.S. Population). Application of the methods described in Section 4.3.4, using the pooled β_mean and power values derived from the bladder cancer dose-response meta-analysis and MLE dose estimates, results in the extra lifetime bladder cancer risks as a function of iAs dose (μg/kg-day) summarized in Table 4-3 and Figure 4-6. Table 4-3 represents the Bayesian hierarchical model estimation of the relationship between μg/kg-day dose and the risk above an estimate of a U.S. risk associated with a zero iAs dose. Table 4-3 presents lifetime extra risk values at various average daily iAs doses ranging from 0 μg/kg-day to 1.0 μg /kg-day, including 0.13 μg/kg-day, which is the total dose associated with

roughly 10 µg/L iAs in drinking water exposure (the current iAs MCL), assuming a 0.011 L/kg-day mean U.S. water consumption rate (U.S. EPA (2019), and a 0.02 µg/kg-day U.S. median dietary background intake.

Table 4-3. Pooled dose-response meta-analysis estimates of extra lifetime bladder cancer incidence risk (per 10,000) at various average daily iAs doses using MLE doses[a, b]

Extra lifetime risk estimates (per 10,000)[a]	Average inorganic arsenic dose (µg/kg-d)[b]													
	0	**0.0365**	**0.06**	**0.1**	**0.13[c]**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
5th %	0	0.002	0.04	0.06	0.08	0.13	0.21	0.29	0.36	0.44	0.53	0.61	0.69	0.78
Mean	0	1.96	3.36	5.88	7.87[d]	12.80	20.50	29.00	38.32	48.53	59.72	72.00	85.47	100.28
95th %	0	5.66	9.61	16.76	22.4	36.66	59.36	85.09	114.35	147.57	184.38	225.41	272.16	324.20

[a]Extra lifetime risks are presented as mean risk with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.

[b]Doses used in EPA modeling. U.S. daily background dose is estimated at 0.0365 µg/kg-day, 0.02 µg/kg-day from diet, 0.0165 µg/kg-day from water and 0 µg/kg-day from air (see Section 4.3.4).

[c]Daily intake associated with the current MCL of 10 µg/L drinking water assuming 0.011 L/kg-day water consumption rate and 0.02 µg/kg-day from diet.

[d] Lifetime extra risks are presented in terms of risk per 10,000 in this table to contextualize the risks in a hypothetical U.S. cohort of 10,000 individuals exposed for a lifetime. A lifetime risk of 7.87 per 10,000 is equivalent to a risk of 0.000787. This illustrative and contextual presentation is not intended to represent a threshold for adversity or recommended risk or action level.

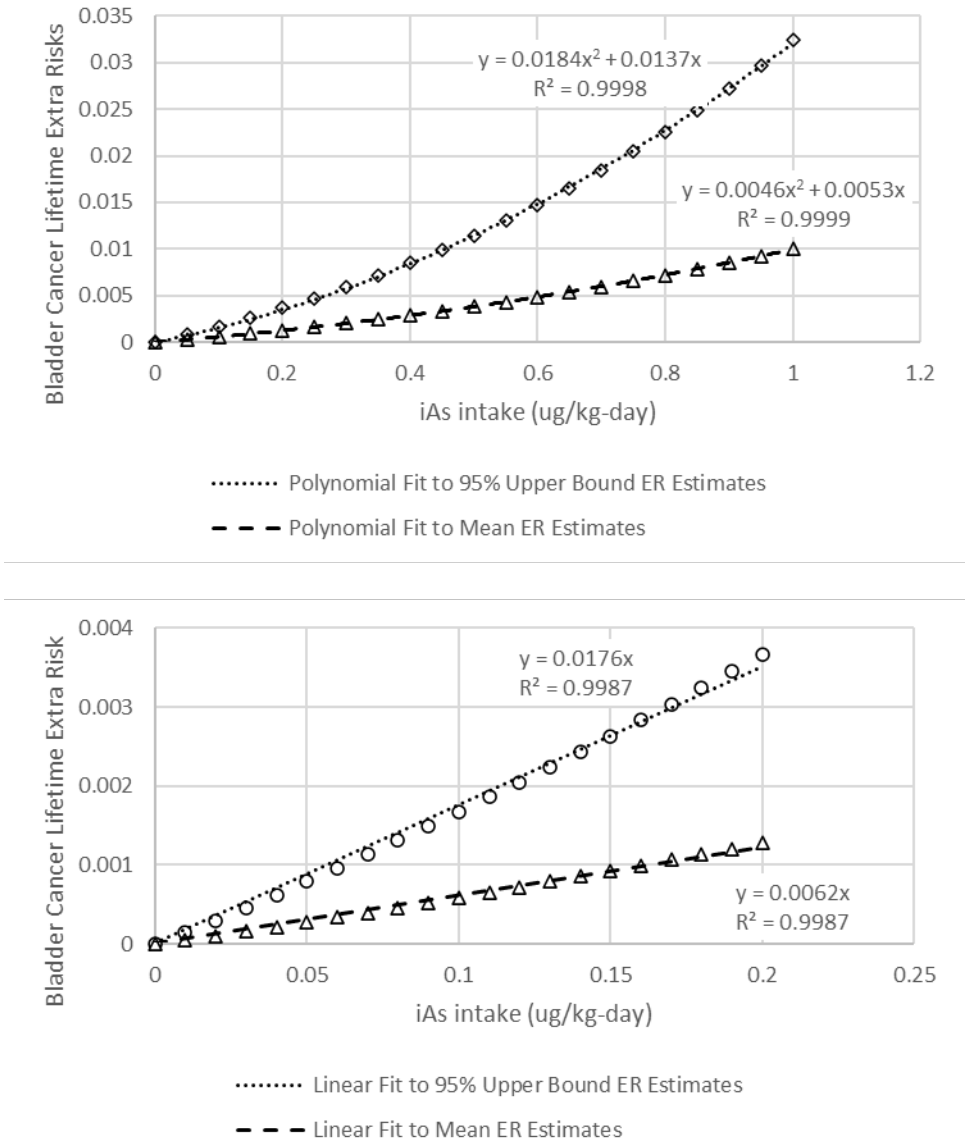


Figure 4-6. U.S. bladder cancer lifetime extra risk versus µg/kg-day iAs doses for doses up to 1.0 µg/kg-day (top plot) and doses up to 0.2 µg/kg-day (bottom plot).

The polynomial and linear trendline formulas given in Figure 4-6 are provided for convenience in approximating a lifetime extra risk at doses and exposures other than those presented in Table 4-3[45]. The slope of the linear trendline for the upper confidence limit (i.e., 95% upper bound on risk; UCL) on the extra risk associated with dose above background is analogous to

[45] The fit of all linear and polynomial bladder cancer trendlines were statistically significant with p-values < 0.0001, as determined by regression analysis in R with the function lm().

the traditional EPA cancer slope factor (CSF).[46] Although EPA's modeling approach in this assessment does not assume linearity in response, a linear trendline slope (1.76×10^{-2} per µg/kg-day) was provided as the CSF below 0.2 µg/kg-day. Mendez et al. (2017) reports that the 95th percent upper bound on drinking water concentrations in the United States is 15.4 µg/L, which translates to approximately 0.19 µg/kg-day iAs daily intake using a 0.011 L/kg-day water consumption rate and accounting for 0.02 µg/kg-day daily iAs exposure via the diet. Therefore, the provided linear CSF below this daily dose covers the majority of drinking water exposure scenarios in the United States. The CSF only provides approximations of the upper-bound lifetime extra risks explicitly calculated using the lifetable approach and using the CSF can result in overestimates of the lifetable risks approximately 20% at very low doses (i.e., 0.005–0.01 µg/kg-day). Given the nonlinearity in upper-bound lifetime extra risks, linear trendlines beyond 0.2 µg/kg-day are associated with increasingly imprecise estimates. For example, a linear trendline up to 0.4 µg/kg-day confers overestimates of risk exceeding 30% at low doses. To account for potential needs to estimate lifetime risks at doses greater than 0.2 µg/kg-day, a polynomial trendline ($risk = 0.0184x^2 + 0.0137x$, where x = dose) is also provided for daily intakes of up to 1.0 µg/kg-day. This polynomial trendline provides more precise approximations of lifetable-calculated lifetime risks, with underestimates of low-dose risk of less than 10%. This polynomial trendline is appropriate for the estimation of risks at doses up to 1.0 µg/kg-day. Table C-31 also provides lifetable-calculated risks at daily intakes of 0 µg/kg-day to 1.5 µg/kg-day, at increments of 0.005 µg/kg-day (i.e., mean and 95% upper-bound lifetime extra risk values are reported for 300 daily intake values). Users that need to generate exact mean or upper-bound lifetime extra risk values at daily intakes other than those reported in Table C-31 can use the Bayesian logistic-power modeling results and lifetable R codes (U.S. EPA, 2025). See the structured workflow, outline, and variable dictionary (U.S. EPA, 2024b) for documentation of modeling files.

Summary of Dose-Response Meta-Analysis of Bladder Cancer Studies

Prior to the modeling the data, the reported exposures from the included studies were converted to estimates of lifetime daily doses of total inorganic arsenic in units of average daily µg iAs per kg body weight (µg/kg-day). Uncertainties in average exposures for the exposure groups and in the conversion to average µg/kg-day daily doses were accounted for, as described in Section 4.3.2. The reported counts of cases (and controls in the instance of case-control studies) were adjusted to account for the effect of covariates. See Appendix C.1.1 (Treatment of Dose Uncertainty; and Adjusting for Covariates) for details.

Following those adjustments, the dose-response meta-analysis approach described in Section 4.3.4 was applied to a set of 11 data sets. On the basis of visual inspection, the model fit was

[46]Traditional cancer slope factors are calculated as $CSF = BMR/BMDL$, where BMR is the benchmark response and BMDL is the 95% one-sided lower confidence limit on the benchmark dose.

considered adequate for all but one dataset.[47] The high dose was dropped to obtain adequate fit for the Steinmaus et al. (2013) dataset because confidence bounds for at least one dose group were outside of the 90% confidence bounds for the dose-response meta-analysis modeling results (see Appendix C.1.2 [Bladder Cancer; Summary of Bladder Cancer Dose-Response Meta-Analysis Results for MLE Dose Estimates]). The choice of a hierarchical structure was supported by the relatively large variation (with mean estimated CV of about 3.7) estimated by the dose-response meta-analysis. The mean of the posterior distribution for β_mean (using the MLE dose estimates) was 0.37 (90% credible interval,[48] 0.004 to 1.03) per μg/kg-day, with an estimated power parameter of 1.09 (95% credible interval, 1.002 to 1.317).

The full β_mean and power parameter posteriors were used to derive a posterior distribution of U.S.-specific lifetime extra-risk estimates via a lifetable analysis using U.S. all-cause mortality and U.S. bladder cancer incidence rates as summarized in Appendix C.1.2 (Extrapolation of Bladder Cancer Risk to Target Population) and in Allen et al. (2020a) and Allen et al. (2020b). As shown in Table 4-3, these U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios (assuming daily intake levels of 0–1.0 μg/kg-day, approximately equivalent to U.S. water iAs exposures of 0–89 μg/ L). At 0.0365 μg/kg-day (estimated background exposure), the mean of the extra lifetime risk distribution was 1.96 per 10,000 (90% credible interval, 0.002 to 5.6 per 10,000). At 0.13 μg/kg-day (daily intake at the current MCL of 10 μg/L), the mean extra lifetime risk was 7.87 per 10,000 (90% credible interval, 0.08 to 22.4 per 10,000).

The above estimates were derived using the MLE doses estimated for study participants. The effect of the uncertainty in those dose values was examined, combining the uncertainty in the means for the exposure-defined groups and in the conversions necessary to obtain a common metric, average μg/kg-day (see Appendix C.1.2 [Bladder Cancer Sensitivity Analyses]). The effect was minimal overall: keeping the estimated power parameter value constant at 1.089, the pooled logistic slope changed from 0.3642[49] to 0.3950 (using systematically lower dose values consistent with the level of uncertainty) or 0.3267 (using systematically higher dose values consistent with the level of uncertainty). The low-end and high-end dose values resulting from a combination of various factors indicate the results are not sensitive to variability/uncertainties in the exposure factors used to estimate the dose levels.

Other sensitivity analyses performed for the bladder cancer dose-response meta-analysis investigated the potential impact of alternative gamma prior distributions for β _mean, the inclusion of a background inhalation exposure, the use of urine biomarker studies, the use of

[47]Model fit to a study's dose-response data was considered to be adequate if the confidence interval for each exposure group response estimate overlapped with the confidence interval for the modeled dose-response curve.
[48]A credible interval is the Bayesian analog to a confidence interval in frequentist statistics.
[49]This bmean value was obtained via Bayesian dose-response analysis with different MCMC settings to minimize computational burden and analysis time (i.e., 25,000 MCMC iterations vs. 50,000). Thus, the bmean reported here is slightly different (0.3642 vs. 0.3694) than the bmean reported in Table 4-2.

alternative exposure metrics or lagged analyses within studies and omitting individual data sets from the analysis (see Appendix C.1.2 [Bladder Cancer Sensitivity Analyses). The sensitivity analysis examining the impact of different gamma prior distributions for β_mean did not result in large differences (≤ 17%; see Appendix C.1.2, Table C-29) in the posterior distributions of the β_mean parameter, indicating that the choice of gamma prior does not substantially influence the estimated association between iAs exposure and bladder cancer in this dose-response meta-analysis. Incorporation of estimates of inhalation exposures in the background estimate of total exposure also did not result in dramatically different (≤0.5%) estimates of extra risk. Consideration of a larger daily background exposure (0.11 μg/kg-day) also had minimal impact on estimated lifetime extra risks at the drinking water standard, only decreasing lifetime extra risks by 4.3%, indicating the lifetable methods used in the assessment are relatively insensitive to the estimates of U.S. background iAs exposure.

When both urine studies are excluded, the mean logistic slope decreased by 59%. This result indicates that the urinary biomarker studies are important drivers of the overall estimated association between iAs exposure and bladder cancer in this dose-response meta-analysis.

Baris et al. (2016) presented multiple results in their study using either total mg or μg/day as the exposure metric and analyses lagged 40 years or unlagged. Table C-30 shows consideration of these alternative data sets in the dose-response meta-analysis did not substantially influence the final modeling; the greatest difference was a 26% decrease in the estimated logistic slope when the 40-year lagged mg exposure metric was used from the Baris study.

Consideration of a normal prior distribution for the pooled slope parameter instead of the gamma distribution (which constrains estimated slope values to be positive) resulted in an increase in mean lifetime extra risks of 14% and 18% at 0.0365 μg/kg-day and 0.13 μg/kg-day daily iAs intake. Use of the logistic model (i.e., power = 1) vs. the logistic-power model resulted in similar increases in lifetime extra risks.

Finally, the influence of the individual studies on the dose-response meta-analysis result (see Table C-28) were tested. With one exception, the effect of removing single studies from the analysis was minimal, with β_mean values differing by less than 20%. The exception was the case-control study of Wu et al. (2013), which is not surprising as this study has the strongest low-dose association between iAs exposure and bladder cancer incidence. In this case, the removal of that study reduced the mean and upper bound β_mean slope estimates by approximately 68%.

In summary, inclusion of a background inhalation exposure had the least (≤0.5%) impact on the β_mean logistic slope estimates for bladder cancer. Exclusion of Wu (68%) or both urinary studies (59%) of urinary biomarker studies would have the greatest impact on the β_mean logistic slope estimates for bladder cancer. The bladder cancer β_mean logistic slope estimates were moderately impacted by exclusion of other studies (≤20%), the Baris et al. (2016) study metric selected (≤30%), variability/uncertainties in the exposure factors (≤16%), alternative gamma prior distributions (≤16%), or using a normal prior for bmean or the logistic model (≤18%).

4.3.6. Bayesian Dose-Response Meta-Analysis Dose-Response Results for Lung Cancer

Bayesian dose-response analyses for lung cancer were conducted as previously described (see Sections 4.3.1 to 4.3.4 and Appendix C.1.1). As discussed in Section 4.3.2, dose-response meta-analyses were performed with low, maximum likelihood, and high dose estimates to investigate dose conversion uncertainties. This section presents the results for dose-response meta-analyses using the MLE doses. The dose-response meta-analyses for lung cancer included both case-control and cohort studies; the six selected studies, converted doses (low, MLE, high) and effective counts used in the lung cancer dose-response meta-analyses are presented in Appendix C.1.2 (Oral Lung Cancer). See U.S. EPA (2025) for access to all dose-response input and output files for lung cancer. U.S. EPA (2024b) provides a structured workflow and variable dictionary for the dose-response files.

In this section, a summary of the results of the lung cancer dose-response meta-analyses using the MLE doses is presented in Table 4-4. The posterior mean for β_sigma is an estimate of the standard deviation of the study-specific β parameter estimates around the estimated mean, β_mean, and is therefore a measure of study-to-study heterogeneity with respect to that key parameter. The posterior mean for β_sigma is 0.313, and its 5th percentile is 0.093 (see Table 4-4). This is associated with a mean coefficient of variation (CV), β_sigma/β_mean, of about 2.08, indicating moderately high heterogeneity. This level of diversity across study slopes justifies the decision to model the slope parameters hierarchically (i.e., a separate slope is derived for each study as opposed to estimating a single, common slope for all data sets). Appendix C.1.2 (Oral Lung Cancer) contains details of the modeling results, including posterior distribution plots for pooled and data-set-specific logistic slope parameters and nonhierarchical and hierarchical model plots for individual studies (see Appendix C.1.2 Oral Lung Cancer; Summary of Lung Cancer Dose-Response Meta-Analysis Results for MLE Dose Estimates) and sensitivity analyses (see Appendix C.1.2 Lung Cancer Sensitivity Analyses).

Table 4-4. Summary of lung cancer (oral exposure) Bayesian analysis output using MLE doses

Parameter	Mean	Standard deviation	5%	95%
β_mean	0.1543	0.1329	0.0040	0.4016
β_sigma	0.3172	0.2117	0.0933	0.7078
β (Argos et al., 2014)	0.0164	0.0113	−0.0007	0.0360
β (García-Esquinas et al., 2013)	0.3542	0.3689	−0.1115	1.0615
β (Chen et al., 2010a)	0.0305	0.0114	0.0123	0.0496
β (Dauphiné et al., 2013)	0.1332	0.1809	−0.1578	0.4401
β (Ferreccio et al., 2000)	0.5003	0.185	0.1991	0.8111
β (Steinmaus et al., 2013)	0.1043	0.028	0.0573	0.1493
power	1.0959	0.0930	1.0053	1.2788

[a]Inference for Stan model: 4 chains, each with iter = 50,000; warmup = 37,500; thin = 1; post-warmup draws per chain = 12,500, total post-warmup draws = 50,000.

Extrapolation of Lung Cancer Risk to Target Population

The posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, and power parameter were used with U.S. all-cause mortality and lung cancer incidence rates as input to a lifetable calculation of the lifetime probability of lung cancer as a function of iAs dose (average μg/kg-day including background levels of U.S. exposure). The methodology is presented in Allen et al. (2020a) and Allen et al. (2020b) and in Appendix C.1.1. The exposure scenario used for these extrapolations posits a continuous, full lifetime exposure to a constant iAs dose.

Age-specific lifetable rates used in the analysis are provided in Appendix C.1.2 (Extrapolation of Lung Cancer Extra Risk to Target U.S. Population). Application of the methods described in Section 4.3.4, using the pooled β_mean values derived from the lung cancer dose-response meta-analysis and MLE dose estimates, results in the extra lifetime cancer risks as a function of iAs dose (μg/kg-day) summarized in Table 4-5 and Figure 4-7. Table 4-5 represents the Bayesian hierarchical model estimation of the relationship between μg/kg-day dose and the risk above an estimate of a U.S. risk associated with a zero iAs dose. Table 4-5 presents lifetime extra risk values at various average daily iAs doses ranging from 0 μg/kg-day to 1.0 μg/kg-day, including 0.13 μg/kg-day, which is the total dose associated with roughly 10 μg/L iAs in drinking water exposure (the current iAs MCL), assuming a 0.011 L/kg-day mean U.S. water consumption rate (U.S. EPA (2019), and a 0.02 μg/kg-day U.S. median dietary background intake.

Table 4-5. Pooled dose-response meta-analysis estimates of extra lifetime lung cancer incidence risk (per 10,000) at various average daily iAs doses

Extra lifetime risk estimates (per 10,000)[a]	Average inorganic arsenic dose (µg/kg-d)[b]													
	0	**0.0365[b]**	**0.06**	**0.1**	**0.13[c]**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
5th %	0	0.06	0.10	0.18	0.25	0.40	0.62	0.85	1.09	1.34	1.60	1.85	2.11	2.37
Mean	0	2.56	4.36	7.56	10.05[d]	16.09	25.20	34.79	44.83	55.31	66.23	77.58	89.37	101.61
95th %	0	7.17	12.08	20.72	27.42	43.68	68.32	94.16	121.51	150.35	180.48	212.14	245.11	279.69

[a]Extra lifetime risks are presented as mean risk with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.

[b]Doses used in EPA modeling. U.S. daily background dose is estimated at 0.0365 µg/kg-day, 0.02 µg/kg-day from diet, 0.0165 µg/kg-day from water and 0 µg/kg-day from air (see Section 4.3.4).

[c]Daily intake associated with the current MCL of 10 µg/L drinking water assuming 0.011 L/kg-day water consumption rate and 0.02 µg/kg-day from diet.

[d] Lifetime extra risks are presented in terms of risk per 10,000 in this table to contextualize the risks in a hypothetical U.S. cohort of 10,000 individuals exposed for a lifetime. A lifetime risk of 10.05 per 10,000 is equivalent to a risk of 0.001005. This illustrative and contextual presentation is not intended to represent a threshold for adversity or recommended risk or action level.

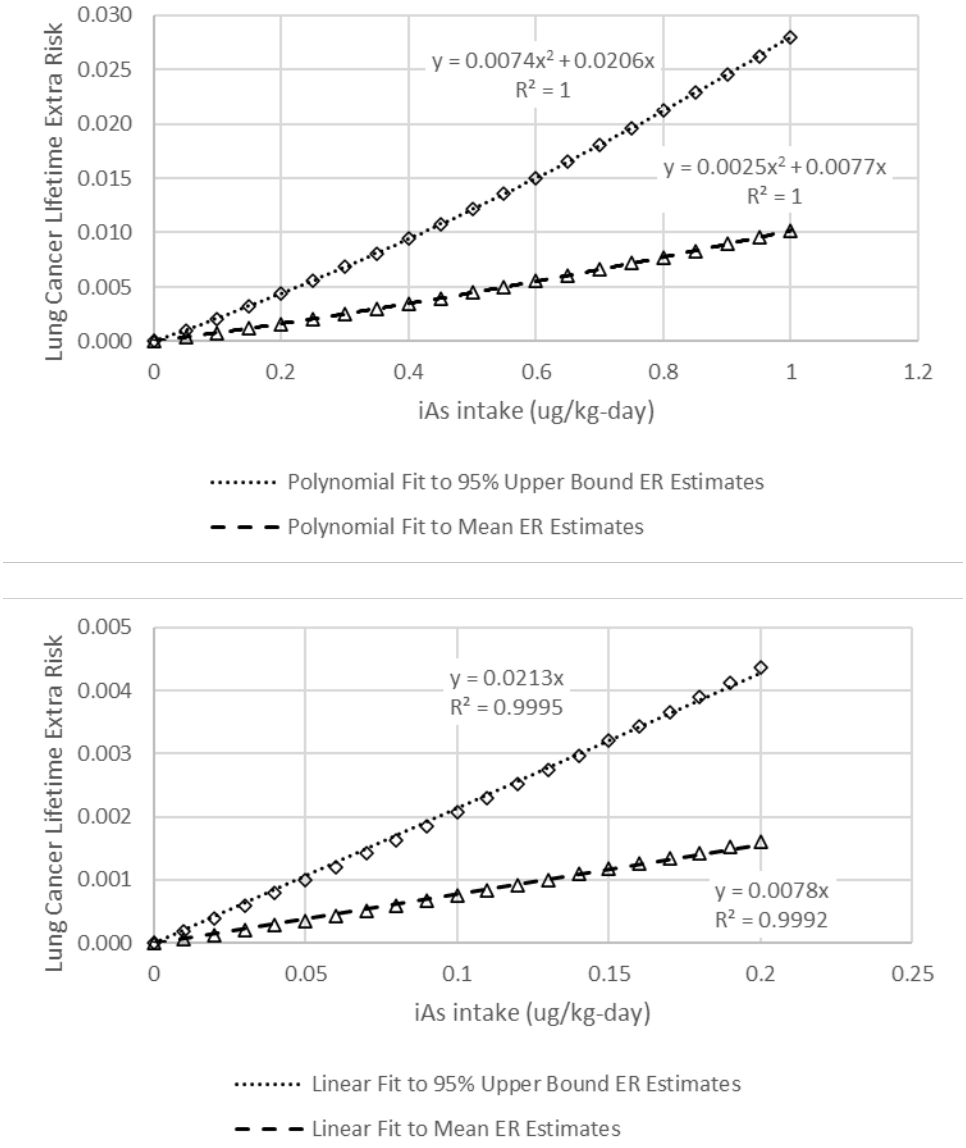


Figure 4-7. U.S. lung cancer lifetime extra risk versus µg/kg-day iAs doses for doses up to 1.0 µg/kg-day (top plot) and doses up to 0.2 µg/kg-day (bottom plot).

The polynomial and linear trendline formulas given in Figure 4-7 are provided for convenience in approximating a lifetime extra risk at doses and exposures other than those presented in Table 4-5[50]. The slope of the linear trendline for the upper confidence limit (i.e., 95% upper bound on risk, UCL) on the extra risk associated with dose above background is analogous to

[50] The fit of all linear and polynomial lung cancer trendlines were statistically significant with p-values < 0.0001, as determined by regression analysis in R with the function lm().

the traditional EPA cancer slope factor (CSF).[51] Although EPA's modeling approach in this assessment does not assume linearity in response, a linear trendline slope (2.13×10^{-2} per µg/kg-day) was provided as the CSF below 0.2 µg/kg-day (see Section 4.3.5 for the rationale for this cut-off value). The CSF only provides approximations of the upper-bound lifetime extra risks explicitly calculated using the lifetable approach and use of the CSF can result in overestimates of the lifetable risks exceeding 15% at very low doses (e.g., 0.005 µg/kg-day). Given the nonlinearity in lifetime extra risks, linear trendlines beyond 0.2 µg/kg-day are associated with increasingly imprecise estimates. For example, a linear trendline up to 0.4 µg/kg-day confers overestimates of risk exceeding 20% at low doses. To account for the need to estimate lifetime risks at doses greater than 0.2 µg/kg-day, a polynomial trendline ($risk = 0.0074x^2 + 0.0206x$, where x = dose) is also provided for daily intakes of up to 1.0 µg/kg-day. This polynomial trendline provides more precise approximations of lifetable-calculated lifetime risks, with overestimates of low-dose risk of approximately 10%. This polynomial trendline is appropriate for the estimation of risks at doses up to 1.0 µg/kg-day. Table C-41 also provides lifetable-calculated risks at daily intakes of 0 µg/kg-day to 1.5 µg/kg-day, at increments of 0.005 µg/kg-day (i.e., mean and 95% upper bound lifetime extra risk values are reported for 300 daily intake values). Users that need to generate exact mean or upper-bound lifetime extra risk values at daily intakes other than those reported in Table C-41 can use the Bayesian logistic-power modeling results and lifetable R codes (U.S. EPA, 2025). See the structured workflow, outline, and variable dictionary (U.S. EPA, 2024b) for documentation of modeling files.

Summary of Dose-Response Meta-Analysis of Lung Cancer Studies (Oral Exposure)

Prior to the analysis, the reported exposures from the included studies were converted to estimates of lifetime daily doses of total inorganic arsenic in units of average daily µg iAs per kg body weight (µg/kg-day). Uncertainties in average exposures for the exposure groups and in the conversion to average µg/kg-day doses were accounted for, as described in Section 4.3.2. The reported counts of cases (and controls in the instance of case-control studies) also were adjusted to account for the effect of covariates.

Given those adjustments, the dose-response meta-analysis approach described in Section 4.3.4 was applied to six data sets. On the basis of visual inspection, the model fit was considered adequate for all but one dataset. The high dose was dropped to obtain adequate fit for the Ferreccio et al. (2000) dataset because confidence bounds for at least one dose group were outside of the 90% confidence bounds for the dose-response meta-analysis modeling results (see Appendix C.1.2 [Summary of Lung Cancer Dose-Response Meta-Analysis Results for MLE Dose Estimates]). The choice of a hierarchical structure was supported by the moderately large variation (with mean estimated CV of about 2.3) estimated by the dose-response meta-analysis. The mean of the

[51]Traditional cancer slope factors are calculated as $CSF = BMR/BMDL$, where BMR is the benchmark response and BMDL is the 95% one-sided lower confidence limit on the benchmark dose.

posterior distribution for β_mean (using the MLE doses) was 0.1543 (90% credible interval, 0.004 to 0.4016) per μg/kg-day, with an estimated power parameter of 1.0959 (95% credible interval: 1.0026 to 1.3387).

The full β_mean and power parameter posteriors (using the MLE doses) were used to derive a posterior distribution of U.S.-specific lifetime extra-risk estimates via a lifetable analysis using U.S. all-cause mortality and U.S. lung cancer incidence rates as summarized in Appendix C.1.2 (Extrapolation of Lung Cancer Risk to Target U.S. Population) section. As shown in Table 4-5, these U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios incorporating background iAs exposure (assuming daily intake levels of 0–1.0 μg/kg-day, approximately equivalent to U.S. water iAs exposures of 0–89 μg/L). At 0.0365 μg/kg-day (estimated background exposure), the mean of that extra lifetime risk distribution was 2.56 per 10,000 (90% credible interval, 0.06 to 7.17 per 10,000). At 0.13 μg/kg-day (daily intake at the current MCL of 10 μg/L), the mean extra lifetime risk was 10.1 per 10,000 (90% credible interval, 0.25 to 27.42 per 10,000).

The above estimates were derived using the MLE doses for study participants. The effect of the uncertainty in those dose values was examined, combining the uncertainty in the means for the exposure-defined groups and in the conversions necessary to obtain a common metric, average μg/kg-day. The effect was minimal overall: keeping the estimated power parameter value constant at 1.0959, the pooled logistic slope changed from 0.1522[52] to 0.1989 (an increase of 31% using systematically lower dose values consistent with the level of uncertainty) or 0.1161 (a decrease of 24% using systematically higher dose values consistent with the level of uncertainty). This finding indicates that the results are not overly sensitive to variability/uncertainties in the exposure factors used to estimate the dose levels.

Other sensitivity analyses performed for the lung cancer dose-response meta-analysis investigated the potential impact of alternative gamma prior distributions for β _mean, the inclusion of a background inhalation exposure, the use of urine biomarker studies, and omitting individual data sets from the analysis (see Appendix C.1.2 [Lung Cancer Sensitivity Analyses]). The sensitivity analysis examining the impact of different gamma prior distributions for β_mean did not result in major differences in the posterior distributions of the β_mean parameter (≥15%, see Appendix C.1.2, Table C-40). Incorporation of estimates of inhalation exposures in the background estimate of total exposure also did not result in appreciable different estimates of extra risk (≥0.2%). Consideration of a larger daily background exposure (0.11 μg/kg-day) also had minimal impact on estimated lifetime extra risks at the drinking water standard, only decreasing lifetime extra risks by 1.8%, indicating the lifetable methods used in the assessment are relatively insensitive to the estimates of U.S. background iAs exposure.

[52]This bmean value was obtained via Bayesian dose-response analysis with different MCMC settings to minimize computational burden and analysis time (i.e., 25,000 MCMC iterations vs. 50,000). Thus, the bmean reported here is slightly different (0.1522 vs. 0.1543) than the bmean reported in Table 4-4.

Excluding the two urine studies increased the mean logistic slope by approximately 10%. The two studies influenced the analysis in opposite directions, with the exclusion of Argos et al. (2014) increasing the slope by 35% and the exclusion of García-Esquinas et al. (2013) decreasing the slope by 18%. These results indicate that the urinary biomarker studies are not substantial drivers of the overall estimated association between iAs exposure and lung cancer in this dose-response meta-analysis.

Consideration of a normal prior distribution for the pooled slope parameter instead of the gamma distribution (which constrains estimated slope values to be positive) resulted in an increase in mean lifetime extra risks of 35% and 34% at 0.0365 μg/kg-day and 0.13 μg/kg-day daily iAs intake. Use of the logistic model (i.e., power = 1) vs. the logistic-power model resulted in similar increases in lifetime extra risks.

Finally, the influence of the individual studies on the dose-response meta-analysis result (see Appendix C.1.2, Table C-39) were tested. Across most included studies, the effect of removing single studies from the analysis was minimal to moderate, with changes to the β_mean logistic slope not exceeding 35%. The study that influenced the analysis the most (i.e., its removal changed the pooled estimate of the β_mean parameter the most) was the data set from the Ferreccio study. In this case, the removal of the study reduced the mean of the β parameter by 65%.

In summary, inclusion of a background inhalation exposure had the least (≤0.4%) impact on the β_mean logistic slope estimates for lung cancer. Study selection has the potential to have the greatest (≤65%) impact on the β_mean logistic slope estimates for lung cancer. The lung cancer β_mean logistic slope estimates were moderately impacted by variability/uncertainties in the exposure factors (≤31%), alternative gamma prior distributions (≤15%), the use of urine biomarker studies (≤10%) or using a normal prior for bmean or the logistic model (≤35%).

4.3.7. Bayesian Dose-Response Meta-Analysis Dose-Response Results for IHD

Bayesian dose-response analyses for IHD were conducted as previously described (see Sections 4.3.1 to 4.3.4 and Appendix C.1.1). As discussed in Section 4.3.2, EPA performed dose-response meta-analyses with low, maximum likelihood, and high dose estimates to investigate dose conversion uncertainties. This section presents the results for dose-response meta-analyses using the MLE doses. The dose-response meta-analyses for IHD included both case-control and cohort studies. Appendix C.1.2 (Ischemic Heart Disease [IHD] Incidence) describes the selected studies, converted doses (low, MLE, high), and effective counts used in the IHD dose-response meta-analyses, detailed modeling results using MLE doses, and sensitivity analyses. See U.S. EPA (2025) for access to all dose-response input and output files for IHD. U.S. EPA (2024b) provides a structured workflow and variable dictionary for the dose-response files.

Table 4-6 presents summary results for the IHD analysis, using the MLE doses. The posterior mean for β_sigma is an estimate of the standard deviation of the study-specific β parameter estimates around the estimated mean, β_mean, and is therefore a measure of study-to-study heterogeneity with respect to that key parameter. The posterior mean for β_sigma is 0.4652,

and its 5th percentile is 0.087 (see Table 4-6). This is associated with a mean coefficient of variation (CV), β_sigma/β_mean, of about 1.78, indicating moderately high heterogeneity. This level of diversity across study slopes justifies the decision to model the slope parameters hierarchically (i.e., a separate slope is derived for each study as opposed to estimating a single, common slope for all data sets). Appendix C.1.2 (Summary of IHD Dose-Response Meta-Analysis Results for MLE Dose Estimates) contains details of the modeling results, including posterior distribution plots for pooled and data-set-specific logistic slope parameters and nonhierarchical and hierarchical model plots for individual studies and sensitivity analyses (see Appendix C.1.2 [IHD Sensitivity Analyses]).

Table 4-6. Summary of Bayesian analysis output for IHD, focusing on key parameters for risk estimation in the target population using MLE doses

Parameter	Mean	Standard deviation	5%	95%
β_mean	0.2602	0.2157	0.0096	0.6679
β_sigma	0.4652	0.392	0.0870	1.1798
(Chen et al., 2013c)	0.0298	0.0157	0.0062	0.0572
(James et al., 2015)	0.7194	0.5394	0.0404	1.7505
(Moon et al., 2013)	0.4113	0.2154	0.0701	0.7780
(Wu et al., 2010b)	0.1564	0.0732	0.0416	0.2819
(Wade et al., 2015)	0.3614	0.2002	0.0640	0.7165
power	1.1191	0.1133	0.10068	1.3438

[a]Inference for Stan model: 4 chains, each with iter = 50,000; warmup = 37,500; thin = 1; post-warmup draws per chain = 12,500, total post-warmup draws = 50,000.

Extrapolation of IHD Risk to Target U.S. Population

Because information on IHD rates across age groups is not available to populate a lifetable, the posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, along with the power parameter, was used with a summary value for the U.S. lifetime probability of developing IHD to estimate the lifetime probability developing IHD as a function of iAs dose (average μg/kg-day, including estimated background iAs intake). The methodology is described by Allen et al. (2020a) and Allen et al. (2020b). The exposure scenario used for these extrapolations posits a continuous, full lifetime exposure to a constant (i.e., daily) iAs dose. The IHD background lifetime probabilities used in the analyses are estimated to be 40% (Lloyd-Jones et al., 1999).[53]

[53]Lloyd-Jones et al. (1999) reported lifetime risks of IHD (CHD) at an index age of 40 years for men (48.6%) and women (31.7%) enrolled in large Framingham Heart Study.

Using the β_mean values derived for the MLE set of dose estimates from the studies selected for the dose-response meta-analyses results in extra lifetime IHD risks as a function of iAs dose (μg/kg-day), summarized in Table 4-7 and Figure 4-8. Table 4-7 represents the Bayesian hierarchical model estimation of the relationship between μg/kg-day dose and the risk above an estimate of a U.S. risk associated with a zero iAs dose. Table 4-7 presents lifetime extra risk values at various average daily iAs doses ranging from 0 μg/kg-day to 1.0 μg/kg-day, including 0.13 μg/kg-day, which is the total dose associated with roughly 10 μg/L iAs in drinking water exposure (the current iAs MCL), assuming a 0.011 L/kg-day mean U.S. water consumption rate (U.S. EPA (2019), and a 0.02 μg/kg-day U.S. median dietary background intake.

Table 4-7. Pooled dose-response meta-analysis estimates of extra lifetime IHD risk (per 10,000) at various average daily iAs doses using MLE doses[a, b]

Extra lifetime risk estimates (per 10,000)[a]	Average inorganic arsenic dose (μg/kg-d)[b]											
	0	**0.1**	**0.13[c]**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
5th %	0	2.70	3.68	6.05	9.70	13.54	17.46	21.54	25.64	29.86	34.11	38.41
Mean	0	82.50	109.96[d]	176.57	276.42	380.50	487.94	598.16	710.68	825.11	941.11	1058.35
95th %	0	219.24	290.59	462.42	719.83	988.38	1262.91	1546.94	1836.55	2131.07	2431.59	2733.85

[a]Extra lifetime risks are presented as mean risk with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.

[b]Doses used in EPA modeling. U.S. daily background dose is estimated at 0.0365 μg/kg-day, 0.02 μg/kg-day from diet, 0.0165 μg/kg-day from water and 0 μg/kg-day from air (see Section 4.3.4).

[c]Daily intake associated with the current MCL of 10 μg/L drinking water assuming 0.011 L/kg-day water consumption rate and 0.02 μg/kg-day from diet.

[d] Lifetime extra risks are presented in terms of risk per 10,000 in this table to contextualize the risks in a hypothetical U.S. cohort of 10,000 individuals exposed for a lifetime. A lifetime risk of 109.96 per 10,000 is equivalent to a risk of 0.010996. This illustrative and contextual presentation is not intended to represent a threshold for adversity or recommended risk or action level.

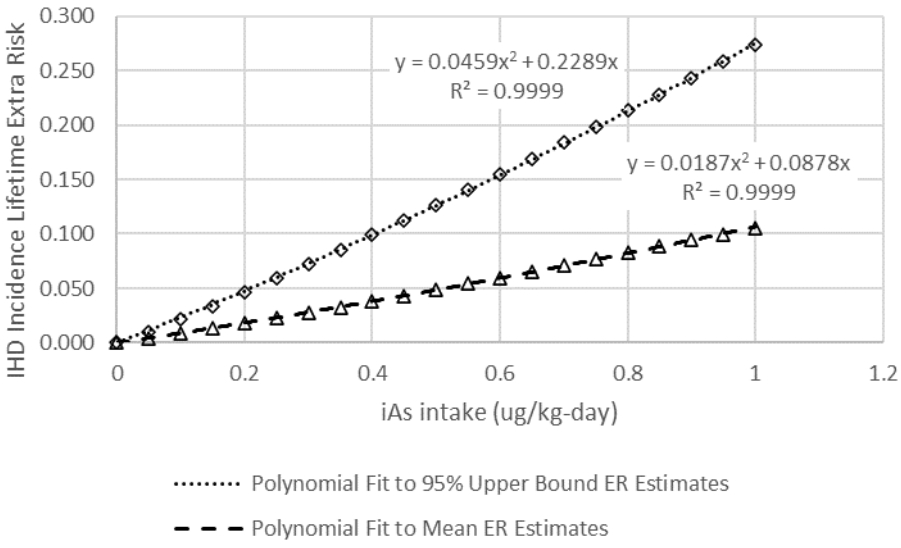


Figure 4-8. U.S. IHD lifetime extra risk versus µg/kg-day MLE doses for all doses. See Section 4.3.4 for discussion of 0.0365 µg/kg-day U.S. background dose estimate.

The polynomial trendline formulas given in Figure 4-8 are provided for convenience in approximating a lifetime extra risk at doses and exposures other than those presented in Table 4-7[54]. The polynomial trendline for the upper-bound lifetime extra risks ($risk = 0.0459x^2 + 0.2289x$, where x = dose) only provide an approximation of the upper-bound lifetime extra risks explicitly calculated using the lifetable approach and use of the trendline can result in overestimates of the lifetable risks exceeding 15% at very low doses (e.g., 0.005 µg/kg-day). This polynomial trendline is appropriate for the estimation of risks at doses up to 1.0 µg/kg-day. Table C-59 also provides lifetable-calculated risks at daily intakes above the RfD, from 0.065 µg/kg-day to 1.5 µg/kg-day, at increments of 0.005 µg/kg-day (i.e., mean and 95% upper-bound lifetime extra risk values are reported for >280 daily intake values). Users that need to generate exact mean or upper-bound lifetime extra risk values at daily intakes other than those reported in Table C-59 can use the Bayesian logistic-power modeling results and lifetable R codes (U.S. EPA, 2025). See the structured workflow, outline, and variable dictionary (U.S. EPA, 2024b) for documentation of modeling files.

Summary of Dose-Response Meta-Analysis of IHD Studies

General limitations and uncertainties associated with the studies used in the IHD dose-response meta-analyses were discussed in Section 4.3.1. As for the bladder cancer and lung cancer dose-response meta-analyses, the exposure information from studies used in the dose-response meta-analyses were converted to estimates of lifetime daily doses of total iAs in units of average

[54] The fit of all polynomial IHD trendlines were statistically significant with p-values < 0.0001, as determined by regression analysis in R with the function lm().

µg iAs per kg body weight (µg/kg-day). Uncertainties in average lifetime daily doses for the exposure groups and in the conversion to µg/kg-day were accounted for, as described in Section 4.3.2, and the reported counts of cases (and controls in the instance of case-control studies) were adjusted to account for the effect of covariates (see Appendix C.1.1 [Treatment of Dose Uncertainty] and Appendix C.1.1 [Adjusting for Covariates] for details).

Following those adjustments, the dose-response meta-analysis approach described in Section 4.3.4 was applied to a set of five data sets. On the basis of visual inspection, the model fit was considered adequate for all but one dataset. The high dose was dropped to obtain adequate fit for the Wu et al. (2010b) dataset because confidence bounds for at least one dose group were outside of the 90% confidence bounds for the dose-response meta-analysis modeling results (see Appendix C.1.2 [Summary of IHD Dose-Response Meta-Analysis Results for MLE Dose Estimates]). The choice of a hierarchical structure was supported by the relatively large variation (with mean estimated CV of about 1.7) estimated by the dose-response meta-analysis. The mean of the posterior distribution for β_mean (using the MLE dose estimates) was 0.26 (90% credible interval,[55] 0.01 to 0.67) per µg/kg-day, with an estimated power parameter of 1.12 (95% credible interval, 1.003 to 1.42).

The full β_mean and power parameter posteriors were used to derive a posterior distribution of U.S.-specific lifetime extra-risk estimates via a lifetable analysis using a summary value for the U.S. lifetime probability of developing IHD as summarized in Appendix C.1.2 (Ischemic Heart Disease (IHD); Extrapolation to Targe U.S. Population) section and by Allen et al. (2020a) and Allen et al. (2020b). As shown in Table 4-7, these U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios (assuming daily intake levels of 0–1.0 µg/kg-day, approximately equivalent to U.S. water iAs exposures of 0–89 µg/L). At 0.13 µg/kg-day (daily intake at the current MCL of 10 µg/L), the mean extra lifetime risk was 110 per 10,000 (90% credible interval, 3.7 to 290.6 per 10,000).

The above estimates were derived using the MLE doses estimated for study participants. The effect of the uncertainty in those dose values was examined, combining the uncertainty in the means for the exposure-defined groups and in the conversions necessary to obtain a common metric, average µg/kg-day (see Appendix C.1.2 [IHD Sensitivity Analyses]). The effect was minimal overall: keeping the estimated power parameter value constant at 1.1191, the pooled logistic slope changed from 0.2545[56] to 0.2418 (5% decrease using systematically lower dose values consistent with the level of uncertainty) or 0.2001 (21% decrease using systematically higher dose values consistent with the level of uncertainty). The low-end and high-end dose values resulting from a

[55]A credible interval is the Bayesian analog to a confidence interval in frequentist statistics.
[56]This bmean value was obtained via Bayesian dose-response analysis with different MCMC settings to minimize computational burden and analysis time (i.e., 25,000 MCMC iterations vs. 50,000). Thus, the bmean reported here is slightly different (0.2545 vs. 0.2602) than the bmean reported in Table 4-6.

combination of various factors indicate the results are not overly sensitive to variability/uncertainties in the exposure factors used to estimate the dose levels.

Other sensitivity analyses performed for the bladder cancer dose-response meta-analysis investigated the potential impact of alternative gamma prior distributions for β mean, the inclusion of a background inhalation exposure, the use of urine biomarker studies, and omitting individual data sets from the analysis. The sensitivity analysis examining the impact of different gamma prior distributions for β_mean did not result in large differences (≤12%; see Appendix C.1.2, Table C-58) in the posterior distributions of the β_mean parameter, indicating that the choice of gamma prior does not substantially influence the estimated association between iAs exposure and IHD in this dose-response meta-analysis. Incorporation of estimates of inhalation exposures in the background estimate of total exposure also did not result in appreciably different estimates of extra risk (≤0.2%). Consideration of a larger daily background exposure (0.11 μg/kg-day) also had minimal impact on estimated lifetime extra risks at the drinking water standard, only decreasing lifetime extra risks by 1.7%, indicating the lifetable methods used in the assessment are relatively insensitive to the estimates of U.S. background iAs exposure.

Consideration of a normal prior distribution for the pooled slope parameter instead of the gamma distribution (which constrains estimated slope values to be positive) resulted in an increase in mean lifetime extra risks of 28% at 0.13 μg/kg-day daily iAs intake. Use of the logistic model (i.e., power = 1) vs. the logistic-power model resulted in similar increases in lifetime extra risks.

Finally, the influence of the individual studies on the dose-response meta-analysis result (see Table C-57) were tested. With one exception, the effect of removing single studies from the analysis was minimal, with β_mean values differing by less than 35%. The exception was the cohort study of James et al. (2015) which is not surprising as this study reported the highest IHD elevations at low-dose iAs exposures. In this case, the removal of that study reduced the mean β_mean slope estimates by approximately 61%.

In summary, inclusion of a background inhalation exposure had the least (≤0.3%) and the exclusion of James (61%) would have the greatest impact on the β_mean logistic slope estimates for IHD. The IHD β_mean logistic slope estimates were moderately impacted by variability/uncertainties in the exposure factors (≤20%), alternative gamma prior distributions (≤13%), or using a normal prior for bmean or the logistic model (≤28%).

4.3.8. Bayesian Dose-Response Meta-Analysis Dose-Response Results for Diabetes

Bayesian dose-response analyses for diabetes were conducted as previously described (see Sections 4.3.1 to 4.3.4). As discussed in Section 4.3.2, EPA performed dose-response meta-analyses with low, maximum likelihood, and high dose estimates to investigate dose conversion uncertainties. This section presents the results for dose-response meta-analyses using the MLE doses. The dose-response meta-analyses for diabetes included both case-control and cohort studies; the selected studies, converted doses (low, MLE, high), and effective counts used in the diabetes dose-response meta-analyses are presented in Appendix C.1.2 (Diabetes). See U.S. EPA

(2025) for access to all dose-response input and output files for diabetes. U.S. EPA (2024b) provides a structured workflow and variable dictionary for the dose-response files.

A summary of the results of the analyses using the MLE doses is presented in Table 4-8. Plots in Appendix C.1.2 (Diabetes; Summary of Diabetes Dose-Response Meta-Analysis Results for MLE Dose Estimates) provide a comparison of the predicted and observed RRs or ORs for all data sets. The visual fits to all the data sets are adequate.

The posterior mean for β_sigma is an estimate of the standard deviation of the study-specific β parameter estimates around the estimated mean, β_mean, and is therefore a measure of study-to-study heterogeneity with respect to that key parameter. The posterior mean for β_sigma is 0.5680, and its 5th percentile is 0.0179 (see Table 4-8). The mean coefficient of variation (CV), β_sigma/β_mean, is about 1.9, indicating moderately large heterogeneity. This level of diversity across study slopes justifies the decision to model the slope parameters hierarchically (i.e., a separate slope is derived for each study as opposed to estimating a single, common slope for all data sets). Appendix C.1.2 (Diabetes) contains details of the modeling results, including posterior distribution plots for pooled and data-set-specific logistic slope parameters and nonhierarchical and hierarchical model plots for individual studies (see Appendix C.1.2; Summary of Diabetes Dose-Response Meta-Analysis Results for MLE Dose Estimates) and sensitivity analyses (see Appendix C.1.2; Diabetes Sensitivity Analyses).

Table 4-8. Summary of diabetes Bayesian analysis output using MLE dose estimates

Parameter	Mean	Standard deviation	5%	95%
β_mean	0.3056	0.2802	0.0134	0.8414
β_sigma	0.5680	0.8085	0.0179	2.0316
(Grau-Perez et al., 2017)	0.7736	0.9825	−0.0372	2.9589
(James et al., 2013)	0.4816	0.3675	0.0366	1.1974
(Pan et al., 2013b)	0.2467	0.1013	0.0878	0.4205
(Coronado-González et al., 2007)	0.2082	0.0753	0.0886	0.3368
power	1.1278	0.1319	1.0068	1.3764

[a]Inference for Stan model: 4 chains, each with iter = 50,000; warmup = 37,500; thin = 1; post-warmup draws per chain = 12,500, total post-warmup draws = 50,000.

Extrapolation of Diabetes Risk to Target Population

Because information on diabetes incidence rates across age groups is not available to populate a lifetable, the posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, along with the power parameter, was used with a summary value of 40% for

the U.S. lifetime probability of developing type 2 diabetes (Gregg et al., 2014)[57] as the input to a lifetable calculation of the lifetime probability of diabetes as a function of iAs dose (average μg/kg-day). The methodology is presented by Allen et al. (2020a) and Allen et al. (2020b). The exposure scenario used for these extrapolations posits a continuous, full lifetime exposure to a constant iAs (i.e., daily) dose.

Using the β_mean values derived for the MLE set of dose estimates from the studies selected for the dose-response meta-analyses results in extra lifetime diabetes risks as a function of iAs dose (μg/kg-day), summarized in Table 4-9 and Figure 4-9. Table 4-9 represents the Bayesian hierarchical model estimation of the relationship between μg/kg-day dose and the risk above an estimate of a U.S. risk associated with a zero iAs dose. Table 4-9 presents lifetime extra risk values at various average daily iAs doses ranging from 0 μg/kg-day to 1.0 μg/kg-day, including 0.13 μg/kg-day, which is the total dose associated with roughly 10 μg/L iAs in drinking water exposure (the current iAs MCL), assuming a 0.011 L/kg-day mean U.S. water consumption rate (U.S. EPA (2019), and a 0.02 μg/kg-day U.S. median dietary background intake.

Table 4-9. Pooled dose-response meta-analysis estimates of extra lifetime diabetes incidence risk (per 10,000) at various average daily iAs doses and U.S. equivalent drinking water above median U.S. doses and exposures using MLE dose estimates [a,b]

Extra lifetime risk estimates (per 10,000)[a]	Average inorganic arsenic dose (μg/kg-d)[b]											
	0	0.1	0.13[c]	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
5th %	0	3.37	4.65	7.84	12.77	18.11	23.82	29.47	35.34	41.28	47.58	53.73
Mean	0	97.04	129.32[d]	207.62	325.01	447.31	573.38	702.38	833.61	966.49	1100.49	1235.15
95th %	0	273.77	363.77	582.91	907.86	1247.49	1600.01	1962.82	2321.40	2686.37	3050.50	3422.84

[a]Extra lifetime risks are presented as mean risk with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.

[b]Doses used in EPA modeling. U.S. daily background dose is estimated at 0.0365 μg/kg-day, 0.02 μg/kg-day from diet, 0.0165 μg/kg-day from water and 0 μg/kg-day from air (see Section 4.3.4).

[c]Daily intake associated with the current MCL of 10 μg/L drinking water assuming 0.011 L/kg-day water consumption rate and 0.02 μg/kg-day from diet.

[d] Lifetime extra risks are presented in terms of risk per 10,000 in this table to contextualize the risks in a hypothetical U.S. cohort of 10,000 individuals exposed for a lifetime. A lifetime risk of 129.32 per 10,000 is equivalent to a risk of 0.012932. This illustrative and contextual presentation is not intended to represent a threshold for adversity or recommended risk or action level.

[57]For diabetes, age-stratified morbidity and mortality values were not available; therefore, a summary estimate of the lifetime probability of developing type 2 diabetes was used instead. Gregg et al. (2014) reported life risks of diabetes from age 20 for men (40.2%) and women (39.6%) in a large (N = 598, 216) study of National Health Interview Survey participants.

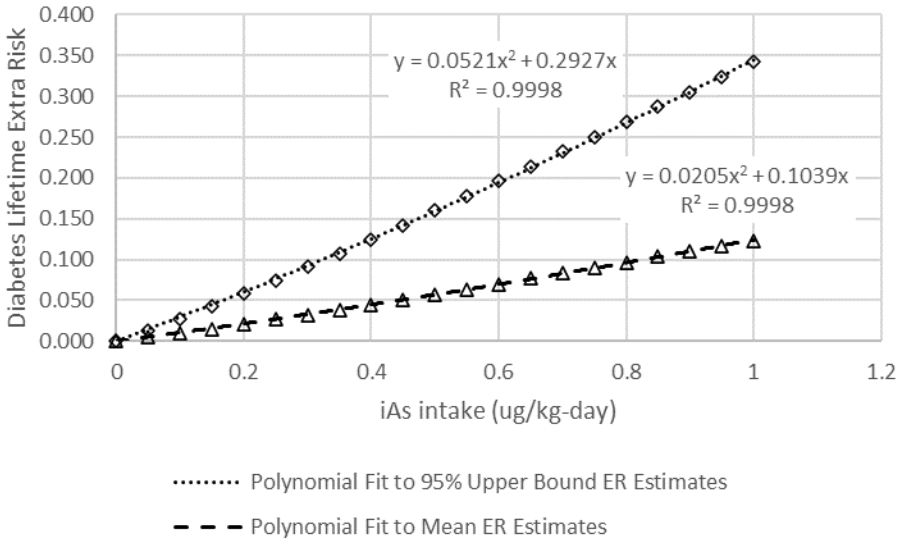


Figure 4-9. U.S. diabetes lifetime extra risk versus µg/kg-day MLE doses for all doses. See Section 4.3.4 for discussion of 0.0365 µg/kg-day U.S. background dose estimate.

The polynomial formulas given in Figure 4-9 are provided for convenience in approximating a lifetime extra risk at doses and exposures other than those presented in Table 4-9[58]. The polynomial trendline for the upper-bound lifetime extra risks ($risk = 0.0521x^2 + 0.2927x$, where x = dose) only provide an approximation of the upper-bound lifetime extra risks explicitly calculated using the lifetable approach and use of the trendline can result in overestimates of the lifetable risks exceeding 20% at very low doses (e.g., 0.005 µg/kg-day). This polynomial trendline is appropriate for the estimation of risks at doses up to 1.0 µg/kg-day. Table C-49 also provides lifetable-calculated risks at daily intakes above the RfD, from 0.065 to 1.5 µg/kg-day, at increments of 0.005 µg/kg-day (i.e., mean and 95% upper-bound lifetime extra risk values are reported for > 280 daily intake values). Users that need to generate exact mean or upper-bound lifetime extra risk values at daily intakes other than those reported in Table C-49 can use the Bayesian logistic-power modeling results and lifetable R codes (U.S. EPA, 2025). See the structured workflow, outline, and variable dictionary (U.S. EPA, 2024b) for documentation of modeling files.

Summary of Dose-Response Meta-Analysis of Diabetes Studies

General limitations and uncertainties associated with the studies used in the diabetes dose-response meta-analyses were discussed in Section 4.3.1. As for the bladder cancer and lung cancer

[58] The fit of all polynomial diabetes trendlines were statistically significant with p-values < 0.0001, as determined by regression analysis in R with the function lm().

dose-response meta-analyses, the exposure information from studies used in the dose-response meta-analyses were converted to estimates of lifetime daily doses of total iAs in units of average µg iAs per kg body weight (µg/kg-day). Uncertainties in average lifetime daily doses for the exposure groups and in the conversion to µg/kg-day were accounted for, as described in Section 4.3.2, and the reported counts of cases (and controls in the instance of case-control studies) were adjusted to account for the effect of covariates (see Appendix C.1.1 [Treatment of Dose Uncertainty] and Appendix C.1.1 [Adjusting for Covariates] for details).

Following those adjustments, the dose-response meta-analysis approach described in Section 4.3.4 was applied to a set of four data sets. On the basis of visual inspection, the model fit was considered adequate for all but one dataset. The high dose was dropped to obtain adequate fit for the Pan et al. (2013b) dataset because confidence bounds for at least one dose group were outside of the 90% confidence bounds for the dose-response meta-analysis modeling results (see Appendix C.1.2 [Summary of Diabetes Dose-Response Meta-Analysis Results for MLE Dose Estimates]). The choice of a hierarchical structure was supported by the relatively large variation (with mean estimated CV of about 1.9) estimated by the dose-response meta-analysis. The mean of the posterior distribution for β_mean (using the MLE dose estimates) was 0.3056 (90% credible interval,[59] 0.0134 to 0.8414) per µg/kg-day, with an estimated power parameter of 1.1278 (95% credible interval, 1.0032 to 1.4754).

The full β_mean and power parameter posteriors were used to derive a posterior distribution of U.S.-specific lifetime extra-risk estimates via a lifetable analysis using a summary value for the U.S. lifetime probability of developing diabetes as summarized in Appendix C.1.2 (Diabetes; Extrapolation to Target U.S. Population) section and by Allen et al. (2020a) and Allen et al. (2020b). As shown in Table 4-9, these U.S.-specific lifetime extra risk estimates were derived for various exposure scenarios (assuming daily intake levels of 0–1.0 µg/kg-day, approximately equivalent to U.S. water iAs exposures of 0–89 µg/L). At 0.13 µg/kg-day (daily intake at the current MCL of 10 µg/L), the mean extra lifetime risk was 129.3 per 10,000 (90% credible interval, 4.7 to 363.8 per 10,000).

The above estimates were derived using the MLE doses estimated for study participants. The effect of the uncertainty in those dose values was examined, combining the uncertainty in the means for the exposure-defined groups and in the conversions necessary to obtain a common metric (i.e., average µg/kg-day) (see Appendix C.1.2 [Diabetes Sensitivity Analyses]). The effect was minimal overall: keeping the estimated power parameter value constant at 1.1278, the pooled logistic slope changed from 0.2999[60] to 0.3586 (using systematically lower dose values consistent with the level of uncertainty) or 0.2516 (using systematically higher dose values consistent with the

[59]A credible interval is the Bayesian analog to a confidence interval in frequentist statistics.
[60]This bmean value was obtained via Bayesian dose-response analysis with different MCMC settings to minimize computational burden and analysis time (i.e., 25,000 MCMC iterations vs. 50,000). Thus, the bmean reported here is slightly different (0.2999 vs. 0.3056) than the bmean reported in Table 4-8.

level of uncertainty). The low-end and high-end dose values resulting from a combination of various factors indicate the results are not overly sensitive to variability/uncertainties in the exposure factors used to estimate the dose levels.

Other sensitivity analyses performed for the diabetes dose-response meta-analysis investigated the potential impact of alternative gamma prior distributions for β _mean, the inclusion of a background inhalation exposure, the use of urine biomarker studies, and omitting individual data sets from the analysis (see Appendix C.1.2 [Diabetes Sensitivity Analysis]). The sensitivity analysis examining the impact of different gamma prior distributions for β_mean did not result in major differences (<10%) in the posterior distributions of the β_mean parameter (see Table C-48). Incorporation of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk (≤0.2%). Consideration of a larger daily background exposure (0.11 μg/kg-day) also had minimal impact on estimated lifetime extra risks at the drinking water standard, only decreasing lifetime extra risks by 2%, indicating the lifetable methods used in the assessment are relatively insensitive to the estimates of U.S. background iAs exposure.

Excluding the two urine studies influenced the analysis in different directions. Excluding the Grau-Perez et al. (2017) studies decreased the slope by 23% and the exclusion of Coronado-González et al. (2007) increased the slope by 49%. These results indicate that the urinary biomarker studies have a low-to-moderate impact on the overall estimated association between iAs exposure and diabetes in this dose-response meta-analysis.

Consideration of a normal prior distribution for the pooled slope parameter instead of the gamma distribution (which constrains estimated slope values to be positive) resulted in an increase in mean lifetime extra risks of 37% at 0.13 μg/kg-day daily iAs intake. Use of the logistic model (i.e., power = 1) vs. the logistic-power model resulted in similar increases in lifetime extra risks.

Finally, the influence of the individual studies on the dose-response meta-analysis result was evaluated. Across all included studies, the effect of removing single studies from the analysis was minimal. The study that most influenced the analysis (i.e., its removal changed the pooled estimate of the β_mean parameter the most) was the Coronado-González et al. (2007) data set. In that case, the removal of the study increased the mean of the β parameter by 49%.

In summary, inclusion of a background inhalation exposure had the least (≤0.2%) and study selection has the potential to have the greatest (≤50%) impact on the β_mean logistic slope estimates for diabetes. The diabetes β_mean logistic slope estimates were moderately impacted by variability/uncertainties in the exposure factors (≤20%), alternative gamma prior distributions (≤10%), or using a normal prior for bmean or the logistic model (≤35%).

4.3.9. Variability and Uncertainty in Bayesian Dose-Response Meta-Analyses

The *EPA IRIS Handbook* (USEPA, 2022), *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), EPA's *Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) all describe factors that commonly

affect the level of variability and uncertainty in dose-response analyses, including consistency in the overall database, dose metrics used for dose-response modeling, model uncertainty, statistical uncertainty in the POD, and uncertainties related to study evaluation such as systematic bias, residual bias, and uncontrolled confounding. This section will qualitatively and, to some extent, quantitatively summarize EPA approaches and sensitivity analysis results that address these factors.

Database Consistency

Evaluation of database consistency is enhanced by EPA's use of only medium or high confidence studies in its dose-response meta-analyses (see study evaluation discussion below). The outcomes selected for dose-response were considered to be generally consistent across studies (see Section 3.2, "Evidence Synthesis:). Concern for inconsistency across studies in dose-response is ameliorated by the use of a meta-analysis, which lessens the impact of a single study's conclusion. EPA's endpoint-specific "leave-one-out" sensitivity analyses were used to the evaluate the consistency of studies within the meta-analyses. The most influential studies, Wu et al. (2013) for bladder cancer and James et al. (2015) for IHD, reduced the mean β_mean slope estimates by 68% and 61%, respectively, when removed. These studies are retained in their respective meta-analyses, however, because their findings are supported by other studies of the same or similar populations. For instance, similarly strong dose-responses for bladder cancer as Wu et al. (2013) have been observed in recent urine studies of the same Taiwan population (Lin et al., 2018; Huang et al., 2018; Chang et al., 2016),[61] and Moon et al. (2013) showed a strong dose-response for IHD in a similar U.S. population as James et al. (2015). The fact that these studies used the same exposure metrics and were conducted in similar study populations suggests that the strong dose-responses observed relative to other studies of the meta-analyses are more likely due to study population differences that result in greater sensitivity to the effect of iAs than study design differences.

Conversion to a Common Dose Metric

EPA converted study-specific exposure metrics to a common μg/kg-day dose metric to allow multiple studies to be combined into a single meta-analysis, thereby increasing the precision and reducing the uncertainty of the dose-response modeling results. When a study offers multiple dose metrics, the choice of study dose metric can be important. Unless a population is limited in its source of fluids (e.g., populations that rely almost exclusively on a single well water source), it is important to survey individuals as to their consumption habits to approximate their actual iAs dose from the water source of interest. For example, Baris et al. (2016) observed distinct differences in their findings for cumulative arsenic intake and average arsenic concentration and noted that this "underscores the importance of incorporating water intake when estimating an individual's total

[61]These studies were not included in the bladder cancer meta-analysis because they were studies of the same population as Wu et al. (2013).

arsenic exposure in low to moderately exposed populations such as that in northern New England." For this reason, EPA prefers cumulative exposure metrics when available and estimates of intake versus drinking water exposure levels.

As described in Appendix C.1.1 (Treatment of Dose Uncertainty), EPA's dose conversion approach uses a probabilistic approach wherein the exposure factors necessary to convert study-specific dose metrics into the unified µg/kg-day dose metric is applied. These exposure factors (e.g., body weight, water consumption rat) were assumed to vary within a population and so distributional representation of this variability were applied via Monte Carlo methods to derive posterior distributions of the unified dose metric. The use of a common dose metric allows for the inclusion of studies that used differing dose metrics, such as urinary or toenail biomarkers, as the exposure assessment method along with studies that assessed exposure on the basis of drinking water intake. Application of the empirical relationship between urinary total As concentration and drinking water iAs exposure (as established by the El-Masri and Kenyon PBPK model (El-Masri and Kenyon, 2008) to urinary biomarker studies is considered to provide reliable estimates of total arsenic dose and average daily lifetime intake (µg/kg-day) (Allen et al., 2020a; Allen et al., 2020b). Urinary arsenic and toenail concentrations integrate all sources of oral exposure at the individual level, accounting for arsenic from both water and diet, an important recommendation of NRC (2013), and are established biomarkers (NRC, 1999; Hughes, 2006; Marchiset-Ferlay et al., 2012).

Derivation of Effective Counts to Address Confounding

Epidemiological studies report adjusted effect measures, adjusted odds ratios (ORs) and Relative Risks (RRs) that retroactively attempt to factor out the effects of potentially confounding variables in order to estimate the effect specifically associated with the exposure of interest, in this case arsenic exposure. As described in Appendix C.1.1, the Bayesian approach that EPA has adopted for the dose-response analysis (Allen et al., 2020b) is based on likelihoods of observing a particular number of cases. A key aspect of the approach is the conversion of reported cases to a count of cases that reflects only the effect of arsenic. To this end, EPA makes use of a studies published adjusted ORs and RRs and associated standard errors (or confidence limits) to derive adjusted counts referred to as "effective count(s)." "Effective counts" are intended to represent the data that would have resulted in the adjusted OR or RR values had confounding not occurred in the study population. While this quantitatively addresses, uncertainty due to confounding, uncertainties related to factors such as systematic bias, residual bias, and uncontrolled confounding must be addressed qualitatively in study-specific risk of bias reviews.

PBPK model

As described in Section 3.1 and the iAs Protocol, Appendix E (link provided in Appendix A), several PBPK models have been developed for evaluating inorganic arsenic exposure. The El-Masri-Kenyon model was chosen as the most appropriate because it incorporates more complex metabolic mechanisms with parameters that were independently derived from experimental and

literature data (Kenyon, 2021). The El-Masri-Kenyon model was evaluated using two large data sets (~11,000 and 500 subjects in Bangladesh and Nevada, respectively) which provided matched individual chronic arsenic drinking water exposure and urinary excretion. Quantitative relationships between exposure in drinking water and urine levels of inorganic arsenic were developed for well-studied populations (Bangladesh, Taiwan, U.S., males and females) using age- and population-specific conversions in the dose estimates. The El-Masri-Kenyon model was considered to adequately predict measured data for the overall oral exposure to inorganic arsenic (El-Masri et al., 2018b; El-Masri et al., 2018a).

Dose-response model uncertainty

As described in detail in Appendix C.1.1, EPA has examined a large collection of alternative models, within the logistic model umbrella. In particular, two sets of models, totaling 39 models in all, were defined in such a way so as to allow for nonmonotonic or threshold-like dose-response shapes. Using bladder cancer, the endpoint with the largest of the dataset of the four meta-analysis endpoints, as a test case, these complex, nonmonotonic models were compared with the simpler logistic model, which does not assume a nonmonotonic shape. While two of the nonmonotonic (fractional polynomial) models resulted in statistically favorable fits to the bladder cancer dataset, they both exhibited biologically unrealistic behavior suggesting that the odds of disease increase to infinity as dose gets close to zero. To avoid this issue without losing the benefits of a more flexible model that can reflect a threshold-like behavior, EPA has developed an approach that addresses the possibility of threshold, or threshold-like, behavior within the logistic model framework. That approach now constitutes the primary analysis approach, i.e., the logistic-power model. This reduces the uncertainty associated in the meta-analysis by extending the range of doses for which the probability of response is essentially the same as the probability of response at 0 μg/kg-day dose. While this model does not allow nonmonotonicity of response, EPA considers it a better approach for exploring and incorporating the possibility of a threshold. One concern with the use of a model with a power term is that it can take on a biologically untenable steep curvature in the low-dose region when attempting to describe dose-response data for which there is little to no difference between the response levels observed at noncontrol doses. This can result in very imprecise BMDs because the data do not constrain the dose-response curve in this lower dose range, where all the change in response is occurring. For this reason, consistent with EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012) constraint recommendation and default settings of the EPA benchmark dose software (BMDS), the power parameter of the logistic-power model used in this assessment is constrained to be 1 or greater. It is recognized that this constraint can result in an underestimation of the true risk for some datasets for which for which there is little to no difference between the response levels observed at noncontrol doses. Conversely, it is recognized that, because no upper-bound constraint is placed on the power parameter, an overestimation of risk can result for datasets that reflect a more shallow to increasing, "hockey-stick" shaped dose-response curvature. Since meta-analyses can conceivably contain datasets with

both attributes (i.e., concave-down plateauing and threshold-like behavior), the concerns over both under- and overestimation of risks should be mitigated.

Statistical Uncertainty in the POD

One measure of statistical uncertainty in the POD is given by the confidence intervals derived from the EPA meta-analyses. The 95th percentile upper bound on the logistic-power model slope estimate serves as the basis for POD estimates used to derive the CSF and RfD estimates for arsenic. A description of the approach for deriving 5th and 95th percentile confidence intervals for EPA meta-analysis dose-response slope estimates are described in Appendix C.1.1. To further assess variability and uncertainty in the POD derivations, EPA conducted comprehensive endpoint-specific sensitivity analyses of factors that can impact the meta-analysis POD derivation. Additional sensitivity analyses performed by EPA for each meta-analysis provide insights into the variability and uncertainty associated with the assumption that the general U.S. population is not appreciably exposed to iAs via inhalation, consideration of a "high-end" estimate for the U.S. background iAs exposure level, considerations of alternative gamma prior distributions for the pooled slope parameter, the use of a prior for the pooled slope that allows negative values, and the calculation of the cancer slope factor with varying numbers of doses. These sensitivity analyses involved comparing the slope derived from the logistic-power model meta-analysis for each endpoint using the mean power parameter estimate derived for that endpoint.

Although inhalation of inorganic arsenic is not considered a primary route of exposure for the general public, the World Health Organization (WHO) estimates that background exposure may range from 0.02 to 0.6 μg/day in areas without substantial arsenic emissions from anthropogenic sources. EPA's sensitivity analysis using these estimates to incorporate inhalation exposures in the background estimate of total exposure did not result in appreciably different estimates of extra risk for any of the four endpoints assessed by meta-analyses.

This assessment uses an assumed background iAs exposure level of 0.0365 μg/kg-day based on a median background dietary exposure level of 0.02 μg iAs/kg-day (Xue et al., 2010) and 0.0165 μg iAs/kg-day from drinking water (estimated from the median U.S. Country average inorganic arsenic drinking water concentration [1.5 μg/L] from USGS data (Mendez et al., 2017) multiplied by the average water intake rate in the U.S. population of 0.011 L/kg-day [U.S. EPA (2019), Table 3-1, "All Ages"]). However, there is some uncertainty in the determination of this background exposure level and different values for the dietary and drinking water components of the estimate could have been used. For example, the mean dietary exposure level of 0.05 μg iAs/kg-day from Xue et al. (2010) could have been used, as well has a higher estimate of drinking water exposure of 0.06 μg iAs/kg-day, sourced from Mantha et al. (2016). Using this "high-end" estimate of 0.11 μg iAs/kg-day for the background iAs exposure only decreases the mean lifetime extra risk at the drinking water standard of 10 μg/L (corresponding to 0.13 μg/kg-day daily intake) less than 5%, indicating that the lifetable methods used are relatively insensitive to the estimates of U.S. background iAs exposure.

The sensitivity analyses of the gamma prior distribution assumption for the β_mean parameter revealed that different gamma prior distributions for β_mean did not result in large differences in the posterior distributions of the β_mean parameter for any endpoint. They also suggest that the results of the meta-analysis are heavily influenced by the actual data being modeled and are not inappropriately driven by the prior assumptions of the Bayesian modeling.

The last sensitivity analysis considered for each endpoint assessed whether the estimation of the cancer slope factor was influenced by the number of risk-at-a-dose values used to characterize the linear trendline. The conclusion drawn from this sensitivity analysis across all endpoints was that the number of risk-at-a-dose values used to define the cancer slope factor appeared to have almost no effect on the estimated slope factor.

Study Evaluation

Study evaluations were performed, and *low* confidence and *uninformative* studies were excluded from the EPA meta-analyses of bladder cancer, lung cancer, diabetes and IHD. The potential for uncontrolled confounding was considered during the study evaluation and reflected in the individual domain ratings relevant to that issue. Details on individual domain and overall confidence ratings for each study are available in HAWC. Overall confidence ratings are holistic judgments based on all domains considered, but studies with critical deficiencies in the confounding domain are not generally considered medium or high confidence. In addition, smoking was considered an essential confounder for study selection for dose-response, i.e., studies that did not control for this factor were excluded.

Concerns regarding uncontrolled confounding, systematic error, or other potential residual bias in a particular study are ameliorated in the dose-response meta-analysis through the use of multiple studies rather than reliance on a single study alone and through the use of sensitivity analyses to explore differences in results based on distinct study approaches. First, meta-analysis allows for the integration of results based on studies with differing strengths and weaknesses, thereby lessening the impact of any particular study's limitations. And second, some sensitivity analyses incorporated into this assessment can be considered a form of triangulation (Lawlor et al., 2016). For example, in sensitivity analyses stratifying by dose metric, results indicated that removal of urinary studies from the lung cancer and diabetes meta-analyses did not change the dose-response slope by more than 20% with the individual studies influencing the results in both directions.

4.3.10. Summary of Bayesian Dose-Response Meta-Analysis Results

Sections 4.3.5 and 4.3.6 present the full details for the dose-response modeling of bladder cancer and lung cancer, respectively, including information on dose-response data set selection, modeling approaches, and detailed results. For all ingestion pathway endpoints, lifetime extra risk estimates are presented in relationship to mean U.S. background rates for bladder cancer incidence and lung cancer incidence of 1.9% and 5.7%, respectively. (see Section 4.3.4). These background

rates are assumed to be associated with median or "typical" U.S. arsenic lifetime daily background intake of 0.0365 μg/kg-day from dietary, drinking water, and air exposure to inorganic arsenic (see Section 4.3.4). Risk at zero iAs dose is estimated so that extra risk above zero iAs dose can be calculated. Extra lifetime risks and 5th and 95th percentile estimates from the dose-response models are presented in Tables 4-3 and 4-5 for bladder cancer and lung cancer, respectively, for a range of arsenic daily intakes, roughly corresponding to a range of daily arsenic intakes up to 1.0 μg/kg-day. For example, at a daily iAs intake of 0.13 μg/kg-day (the total dose associated with roughly 10 μg/L iAs in drinking water assuming a 0.011 L/kg-day water consumption rate and 0.02 μg/kg-day dietary background intake, the lifetime extra risks for bladder cancer and lung cancer are 7.9×10^{-4} (90% CI: 8×10^{-6}-2.2×10^{-3}) and 1.0×10^{-3} (90% CI: 2.5×10^{-5}-2.7×10^{-3}), respectively. For all estimates, including lung cancer from oral exposures, extra risks are calculated assuming zero inhalation exposure.

Polynomial and linear (slope factor) formulas for approximating the predicted means and 5th and 95th percentiles for lifetime extra risk for bladder cancer and lung cancer at any given μg/kg-day dose are presented in the dose-response plots provided in Sections4.3.5 and 4.3.6.[62, 63] Although a nonlinear logistic-power model was used in the dose-response meta-analyses, a linear trendline was provided below 0.2 μg iAs/kg-day dose, given that this dose is assumed to cover the majority of drinking water exposure scenarios in the U.S. (see discussion in Section 4.3.5). For this assessment, the cancer slope factor is defined as the slope of the linear trendline between the estimated 95% upper bound on lifetime extra risk and dose. Defined in this way, the approximate cancer-specific slope factors for bladder cancer and lung cancer are 1.76×10^{-2} $(\mu g/kg\text{-}d)^{-1}$ and 2.13×10^{-2} $(\mu g/kg\text{-}d)^{-1}$, respectively. These CSFs can be multiplied by an estimate of a lifetime oral μg/kg-day dose to approximate a 95% upper-bound lifetime extra risk for the endpoint in question. A combined slope factor of ***3.17×10^{-2} $(\mu g/kg\text{-}d)^{-1}$, representing the risk of developing either tumor,*** was derived assuming that individual tumor risks are normally distributed (see Section 4.9).[64]

[62]To derive the most accurate values, meta-regression models and lifetables should be applied in accordance with methods described by Allen et al. (2020a) and Allen et al. (2020b).

[63]These extra risk estimates assume a constant level of daily lifetime intake. That vulnerable windows of exposure may exist is recognized, as suggested by evidence for magnified cancer, cardiovascular, and neurodevelopmental risks following in utero or early-life arsenic exposure (Yuan et al., 2007; Steinmaus et al., 2013; Farzan et al., 2013a).

[64]Calculated as described in the Toxicological Review of Chloroprene (U.S. EPA, 2010), assuming a normal distribution and using MLE and 95% upper-bound linear slope estimates shown in Figure 4-6 (bladder cancer) and Figure 4-7 (lung cancer). The combined CSF is calculated as $\sum(MLE\ slopes) + 1.645 \times composite\ SD$. The composite SD is equals $\sqrt{\sum variances} = \sqrt{\sum\left(\frac{upper\ bound - MLE}{1.645}\right)^2} = \sqrt{\left(\frac{0.0176-0.0062}{1.645}\right)^2 + \left(\frac{0.0213-0.0078}{1.645}\right)^2} = 0.0107$. Thus, the combined CSF equals $(0.0062 + 0.0078) + (1.645 * 0.0107) = 0.0317$.

Sections 4.3.7, 4.3.8, 4.4, and 4.5 present the full details for the dose-response modeling of ischemic heart disease (IHD), diabetes, fetal, newborn, and infant health outcomes, and developmental neurodevelopmental effects, respectively, including dose-response data set selection, modeling approaches, and detailed results for each endpoint/exposure pathway. RfD derivations are fully described in Section 4.6.

For all ingestion pathway endpoints, lifetime extra risk estimates, calculated using the Bayesian dose-response meta-analysis approach, are presented in relationship to mean U.S. background rates for of 40% for IHD and diabetes outcomes (see Sections 4.3.7 and 4.3.8). These background rates are assumed to be associated with median or "typical" U.S. arsenic lifetime daily background intake of 0.0365 μg/kg-day from dietary, drinking water, and air exposure to inorganic arsenic (see Section 4.3.4). Risk at zero iAs dose is estimated so that extra risk above zero iAs dose can be calculated. Extra risks and 5th and 95th percentile estimates from the dose-response models are presented for a range of daily arsenic intakes up to 1.0 μg/kg-day. For all estimates extra risks are calculated assuming zero inhalation exposure. As an example, at a daily iAs intake of 0.13 μg/kg-day, the lifetime extra risks for IHD and diabetes are 1.1×10^{-2} (90% CI: 3.7×10^{-4}–2.9×10^{-2}) and 1.3×10^{-2} (90% CI: 4.7×10^{-4}–3.6×10^{-2}), respectively. Table 4-10 summarizes the lifetime extra risks estimated at the drinking water standard of 10 μg/L (i.e., 0.13 μg/kg-day) for bladder cancer, lung cancer, IHD, and diabetes.

Table 4-10. Lifetime extra risks at 0.0365 μg/kg-day and 0.13 μg/kg-day for bladder cancer, lung cancer, IHD, and diabetes

Endpoint	Lifetime extra risks (per 10,000) 0.13 μg/kg-d	Trendlines
Bladder cancer	7.87 (90% CI: 0.08, 22.4)	Linear, mean: $y = 0.0062x$ Linear, 95th UB: $y = 0.0176x$ Polynomial, mean: $y = 0.0046x^2 + 0.0053x$ Polynomial, 95th UB: $y = 0.0184x^2 + 0.0137x$
Lung cancer	10.05 (90% CI: 0.25, 27.42)	Linear, mean: $y = 0.0078x$ Linear, 95th UB: $y = 0.0213x$ Polynomial, mean: $y = 0.0025x^2 + 0.0077x$ Polynomial, 95th UB: $y = 0.0074x^2 + 0.0206x$
IHD	109.96 (90% CI: 3.68, 290.59)	Polynomial, mean: $y = 0.0187x^2 + 0.0878x$ Polynomial, 95th UB: $y = 0.0459x^2 + 0.2289x$
Diabetes	129.32 (90% CI: 4.65, 363.77)	Polynomial, mean: $y = 0.0205x^2 + 0.1039x$ Polynomial, 95th UB: $y = 0.0521x^2 + 0.2927x$

4.4. FETAL, NEWBORN, AND INFANT HEALTH OUTCOMES

The basis for study selection for screening analyses of exposure-response for the fetal, newborn, and infant health effects are described by Hobbie et al. (2020), Section 4.2, and Appendix C.2.1. For these effects, the screening-level analyses presented in Section 4.2 indicated Bayesian dose-response meta-analysis approach used for bladder cancer, lung cancer, IHD, and diabetes would not be feasible due to the general lack of dichotomous, relative risk studies for these health outcomes. Additionally, it was unclear how to apply a lifetable approach to estimate risk of birth outcomes, and so a dose-response meta-analysis approach similar to that employed for birth weight in a previous IRIS assessment (U.S. EPA, 2024a) was used. See U.S. EPA (2025) for access to all dose-response input and output files for body weight.

On the basis of literature searches up to August 2022 (see Section 2.1), 80 fetal, newborn, and infant health outcomes *high* or *medium* confidence studies were identified and advanced for consideration for dose-response (see Figure 4-10).

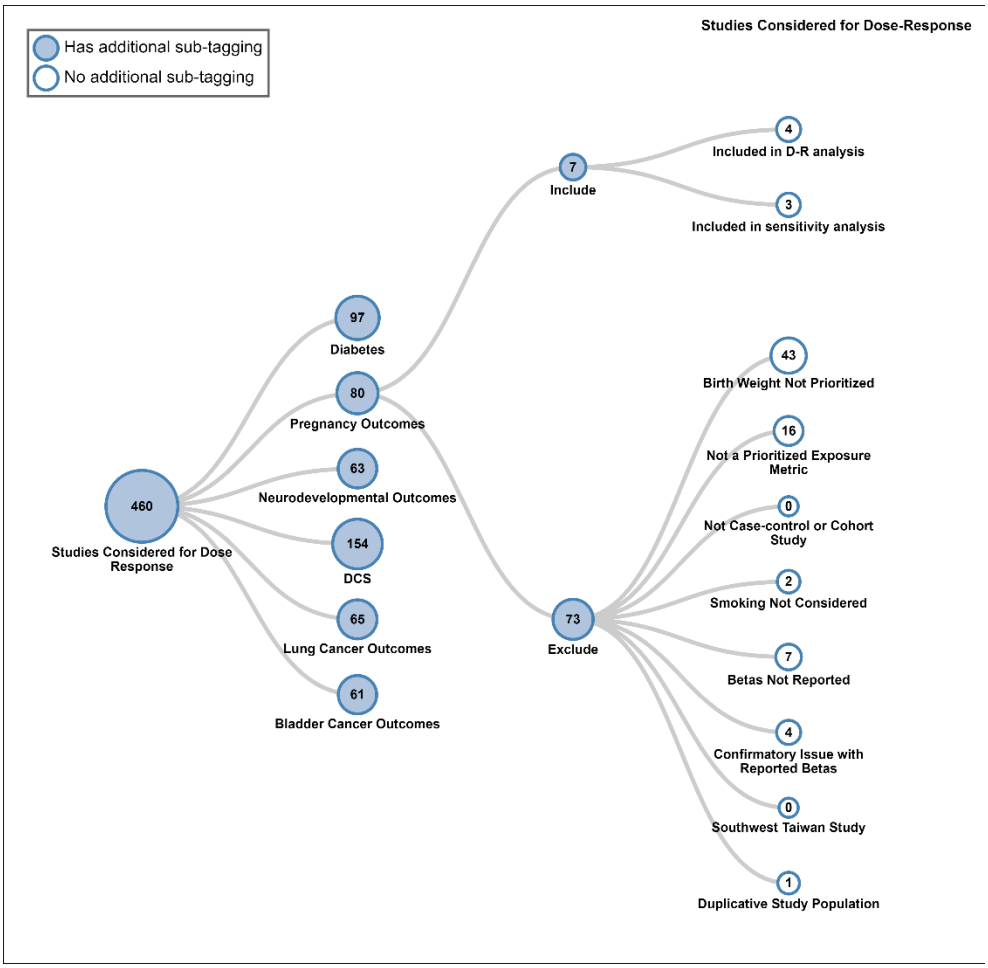


Figure 4-10. Study selection flow for identification of studies for fetal, newborn, and infant health outcomes dose-response analyses (see interactive version in HAWC).

For fetal, newborn, and infant health outcomes, two sub-outcomes reached an evidence synthesis judgment of *moderate*: 1) fetal & infant mortality; 2) birth weight. In general, dose-response modeling on mortality outcomes is not the preferred option when alternatives (especially those that may be more sensitive) are available. Therefore, birth weight was prioritized as the endpoint carried forward for dose-response analysis.

As noted in Section 4.3.1, the dose-response study selection for fetal, newborn, and infant health outcomes now explicitly considers whether a study controlled for maternal smoking or secondhand smoke, given their roles as potential key confounders in the relationship between arsenic and these outcomes (Salihu and Wilson, 2007). In the conduct of the dose-response study-selection process, a study was considered to have addressed smoking if it was reported that mothers in the study did not smoke or were not exposed to secondhand smoke during pregnancy, if a study reported children were not exposed to smoke during early childhood, or if smoking was considered in statistical models as a confounder. If a study did not mention smoking or how the authors addressed confounding due to tobacco smoke exposure and smoking rates in the population were anticipated to be non-negligible, the study was excluded from consideration for dose-response.[65]

Ultimately, seven cohort studies were considered for dose-response analysis of birth weight outcomes (Rahman et al., 2009; Liu et al., 2018; Liao et al., 2018; Laine et al., 2015; Kile et al., 2016; Goodrich et al., 2019; Gilbert-Diamond et al., 2016). Two data sets were from U.S. populations, two were from Bangladesh, and one each were from China, Taiwan, and Mexico. See interactive HAWC figure for full list of which studies were excluded under each selection criterion/consideration. The order of appearance of the criteria/consideration in the HAWC figure above reflects the sequence of application (i.e., confirmation of prioritized endpoint was the first screening criteria). Most studies were excluded because they did not present findings on the prioritized outcome of birth weight or use drinking water or urine as the exposure metric. In other cases, studies were excluded from further analysis because they investigated the effect of iAs on birth weight in a duplicate study population (Rahman et al., 2017b) or reported beta coefficients that were not applicable in the dose-response methods employed by EPA. For example, both Bloom et al. (2015) and Kim et al. (2020) reported beta coefficients for birth weight z-scores, Bloom et al. (2016) reported beta coefficients for tertiles of exposure, not a single beta for the entire population, and Fano-Sizgorich (2021) reported that beta coefficients were estimated with log-transformed urinary tAs concentrations but did not report the base for the log transformation.

Of the studies that reported beta coefficients, only Kile et al. (2016) reported the effect in units of drinking water arsenic (µg/L); all other studies (Rahman et al., 2009; Liu et al., 2018; Liao et al., 2018; Laine et al., 2015; Goodrich et al., 2019; Gilbert-Diamond et al., 2016) reported metrics

[65]In addition to smoking, other important confounders such as race/ethnicity, maternal age, maternal alcohol use, measure of SES (e.g., education/income), infant sex, parity, and maternal BMI were also considered as part of the study evaluation process (see Section 1.6.2 and HAWC for more details).

based on maternal urinary total As concentration (see Table C-63 for study details). For other outcomes in this assessment, use of the El-Masri–Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a) allows for the conversion of urine biomarker data to oral doses. However, there is uncertainty about application of this model to populations of pregnant women, so it was not used for birth weight. Instead, a study by Gilbert-Diamond et al. (2016) that reports the relationship between maternal urinary total As and drinking water concentrations was used to allow for consideration of studies that report maternal urinary concentrations for fetal, newborn, and infant health outcomes. Similarly, studies reporting iAs levels in toenails were not considered for birth weight as the previously discussed algorithm that allows the conversion of toenail iAs concentrations into drinking water concentrations (Moon et al., 2013; Karagas et al., 2002) was only established in adult populations.

EPA additionally considered how each of these studies accounted for gestational age. Given the potential mediating role of gestational age on the association between arsenic and birth weight (Wilcox et al., 2011; Kile et al., 2016), EPA's primary meta-analysis to derive a POD for birth weight was restricted to maternal urinary studies that did not adjust for this variable (Rahman et al., 2009; Liu et al., 2018; Laine et al., 2015). A sensitivity analysis consisting of a meta-analysis with all six maternal urinary studies is additionally reported in the assessment (see Appendix C.2.1). Separately, we also present an individual analysis of the Kile et al. (2016) study, which explored mediation by gestational age through structural equation modeling (SEM). Although Kile et al. (2016) was conducted in a Bangladeshi population, it was considered suitable for deriving a candidate value for the general U.S. population based on it being a medium confidence study with a "definitely low risk of bias" and "probably low risk of bias" determinations for the critical domains concerning confidence in how the study accounted for important confounding variables and exposure assessment, respectively. The study also was found to have a "definitely low risk of bias" for the outcome assessment domain. Regarding this study being conducted in a Bangladeshi population, a potential concern would be whether this study represented a "high-exposure" population compared with a general U.S. populations. While this study was conducted in a population that does have a higher upper bound on exposure than the general U.S. population, the concern appears to be somewhat mitigated by the study authors reporting that "… arsenic exposures were relatively modest with a median concentration of 2.3 μg/L in drinking water at the time of enrollment (interquartile range: 0.9, 36 μg/L)."

4.4.1. Point of Departure Estimation for Birth Weight Studies

Two of the seven studies that made it through study selection used log-transformed arsenic concentrations as the exposure metric: Kile et al. (2016) used natural log-transformed values (i.e., β coefficient = g per ln(μg/L) iAs in drinking water) and Liu et al. (2018) used $\log_2$ transformed values (i.e., β coefficient = g per $\log_2$(μg/L) maternal urinary tAs). In order to use the β coefficients from these studies in a meta-analysis with β coefficients from studies that did not use a log-transformed exposure metrics, the β coefficients for Kile et al. (2016) and Liu et al. (2018) were re-

expressed in terms of per µg/L according to Dzierlenga et al. (2020)[66] For example, Kile et al. (2016) reported a β coefficient of −17.4 g (95% CI: −22.8, −12.0) per ln(µg/L) increase for the association between birth weight and iAs concentrations in drinking water. Given the reported study-specific median (2.3 µg/L) and interquartile range (IQR: 0.9–36 µg/L of exposure, the distribution of exposure was estimated by assuming the exposure follows a log-normal distribution with mean and standard deviation:

$$\mu = ln(q_{50}) = ln(2.3) = 0.83 \quad (4\text{-}2)$$

$$\sigma = ln(q_{75}/q_{25})/1.349 = ln(0.9/36)/1.349 = 2.73 \quad (4\text{-}3)$$

Then, the 25th through 75th percentiles at 10 percentile intervals of the exposure distribution and corresponding responses of reported β coefficient were estimated. The re-expressed β coefficient is determined by minimizing the sum of squared differences between the curves generated by the re-expressed β and the reported β. Doing so results in a re-expressed β coefficient of −3.91 g (95% CI: −5.13, −2.7) per µg/L. The same approach was used to re-express the β coefficient for Liu et al. (2018).

For continuous data, the typically preferred definition of the benchmark response (BMR) includes a consideration of what constitutes a minimal level of change in the endpoint that is biologically significant. For birth weight, there is no accepted percent change that is considered adverse. However, there is a clinical definition of what constitutes an adverse effect for birth weight: babies born weighing less than 2,500 g (5.5 lbs.) are considered low birth weight (WHO, 2004), and low birth weight is associated with a wide range of health conditions throughout life (Hack et al., 1995; Reyes and Mañalich, 2005; Tian et al., 2019).

The CDC Wonder site (https://wonder.cdc.gov/natality.html) provides vital statistics for babies born in the United States and using this data confers multiple benefits. First, in 2018, 3,791,712 live births occurred in the United States, according to final natality data, with a mean birth weight (± standard deviation) of 3,261.6 ± 590.7 g (7.19 ± 1.30 lbs.). Using a dataset with this many subjects ostensibly confers increased precision in estimating the "background" birth weight to use in BMD calculations compared with study-specific estimates of birth weight. Also, the CDC Wonder database can be queried so that the exact percentage of the population falling below the

[66]A recent study examined the uncertainty introduced by the Dzierlenga re-expression method and reported a bias in the direction of a larger effect estimate, i.e., an overestimation of the true effect estimate, when re-expressing from the log scale to the unlogged scale (Linakis et al., 2024). However, EPA noted that in the analyses of real study data, the authors treated the estimated effect estimates, which are random variables, as if they were constants in their Table 4. Comparing point estimates of random variables ignores their variance, and ignoring variance may lead to unsupported conclusions. EPA noted that had the confidence intervals around the point estimates been compared, the observed regression coefficient would fall within the confidence intervals for the re-expressed regression coefficient when study sample sizes were approximately less than n = 3000. The total sample size for the meta-analysis was 2007 individuals, well within the range of study sizes where reported betas and re-expressed betas are statistically consistent. Thus, EPA judged the Dzierlenga methodology for re-expression to be appropriate.

cut-off value for clinical adversity can be determined. One uncertainty in the use of the Wonder site birth weight data for BMR estimation is its appropriateness when using that BMR in conjunction with a beta reported from a non-U.S. study. However, EPA is not aware of any queryable database of birth weight data for the countries used in the birth weight analyses (i.e., Bangladesh, Taiwan, or Mexico). Given this lack of queryable birth weight data in non-U.S. populations, and the intent to derive a POD that is relevant to U.S. populations, use of the Wonder site birth weight data was deemed appropriate for defining the BMR level.

In the 2018 U.S. natality data, 8.27% of live births fell below the public health definition of low birth weight (i.e., 2,500 g). Given the clinical cut-off for adversity (i.e., birth weight below 2,500 g) and the observation that 8.27% of all live U.S. births were below this cut-off in 2018, the hybrid approach (U.S. EPA, 2012) can be used to define the BMR for this continuous endpoint. The hybrid approach harmonizes the definition of the BMR for continuous data with that for dichotomous data, and therefore is an advantageous approach.[67] Essentially, the hybrid approach involves estimating the dose that increases the percentile of responses falling below (or above) some cut-off for adversity in the tail of the response distribution. Application of the hybrid approach requires selecting an extra risk value for BMD estimation as well as the cut-off value for adversity. In the case of birth weight, an extra risk of 5% is selected, given this level of response is typically used when modeling developmental responses from animal toxicological studies and has been used in IRIS assessments when modeling epidemiologic data (U.S. EPA, 2024a), and low birthweight confers increased risk for adverse health effects throughout life, thus supporting a BMR lower than the standard BMR of 10% extra risk. A BMR of 1% might also be considered for such an adverse effect occurring during a sensitive lifestage; however, a 1% BMR is typically reserved for the most severe effects, such as outcomes closely associated with mortality or complete loss of function. Thus, a BMR = 5% extra risk was considered most appropriate.

Therefore, given a background response and a BMR = 5% extra risk, the BMD would be the dose that results in 12.86% of the responses falling below the 2,500 g cut-off value:

$$Extra\ Risk(ER) = (P(d) - P(0)) \,/\, (1 - P(0)) \tag{4-4}$$

$$P(d) = ER(1 - P(0)) + P(0) = 0.05(1 - 0.0827) + 0.0827 = 0.1286 \tag{4-5}$$

Using the mean birth weight for all U.S. births of 3,261.6 g (with a standard deviation of 590.7 g), EPA calculated the mean response that would be associated with the 12.86th percentile of the normal distribution falling below 2,500 g. In this case, the mean birth weight would be 3,169.2 g.

[67]While the explicit application of the hybrid approach has not been commonly used in IRIS dose/concentration/exposure-response analyses, the more commonly used SD-definition of the BMR for continuous data is simply one specific application of the hybrid approach. The SD-definition of the BMR assumes that the cut-off for adversity is the 1.4th percentile of a normally distributed response and that shifting the mean of that distribution by one standard deviation approximates an extra risk of 10%.

The meta-analysis, restricted to the three studies (Rahman et al., 2009; Liu et al., 2018; Laine et al., 2015) that did not control for gestational age, resulted in a pooled β coefficient of −1.28 g per µg/L maternal tAs (95% CI: −2.05, −0.52) (see Appendix C.2.1 for details).[68] The BMD was calculated by rearranging the equation $y = mx + b$ and solving for x, using 3,261.6 g for the b term and −1.28 for the m term. Doing so results in a value of 72.19 µg/L:

$$x = (y - b)/m = (3{,}169.2\ g - 3{,}261.6\ g)/(-1.28\ g(\mu g/L)^{-1}) = 72.18\ \mu g/L \qquad (4\text{-}6)$$

To calculate the BMDL, the method is similar, except the lower limit on the β coefficient is used for the m term. The pooled analysis a two-sided 95% confidence interval for the β coefficient (−2.05, −0.52 g per µg/L), meaning that the lower limit of that confidence interval corresponds to a 97.5% one-sided lower limit. The BMDL is defined as the 95% lower limit of the BMD (i.e., corresponds to a two-sided 90% confidence interval), so the proper lower limit on the β coefficient needs to be calculated before calculating the BMDL. The standard error for the pooled β coefficient is 0.39, meaning that the corresponding 95% one-sided lower bound on the β coefficient can be calculated as:

$$95\%\ one\ sided\ LL = \beta - 1.645\big(SE(\beta)\big) = -1.28\ g(\tfrac{\mu g}{L})^{-1} - 1.645\left(0.39\ g(\tfrac{g}{L})^{-1}\right) = -1.92\ g(\tfrac{\mu g}{L})^{-1} \qquad (4\text{-}7)$$

Using this value for the m term results in a BMDL value of 48 µg/L maternal urinary tAs. Given the BMD and BMDL are in units of µg/L maternal urinary tAS, an approach is needed to convert this dose metric into units of µg/kg-day daily intake. Gilbert-Diamond et al. (2016) investigated the association of drinking water ingestion and rice consumption on maternal urinary tAs concentration; applying equation Eq. 52 (see Appendix C.2.1), and adjusting for body weight, a BMD of 1.59 µg/kg-day and a BMDL of 1.4 µg/kg-day were derived for the three-study meta-analysis.

The same procedure was used to estimate a BMD and BMDL from the β coefficient reported in Kile et al. (2016) (modeled individually as it was the only birth weight drinking water study), re-expressed to the normal scale (beta: −3.91 g per µg/L, 95% CI: −5.13, −2.7). Using this beta and its 95% one-sided confidence interval (calculated as above) results in BMD of 23.6 µg/L and a BMDL of 18.7 µg/L. The BMD and BMDL, in units of µg/L drinking water, was then converted into units of µg/kg-day daily intake by multiplying by 0.01 L/kg-day, the mean U.S. water consumption rate for pregnant women (U.S. EPA, 2019), Table 3-62, "Community Water") and adding a 0.05 µg/kg-day median U.S. dietary background dose (Xue et al., 2010). This results in a BMD and BMDL in units of daily intake of 0.286 µg/kg-day and 0.237 µg/kg-day, respectively.

[68]A sensitivity analysis in which studies that controlled for gestational age in their statistical analyses resulted in a slightly attenuated pooled effect compared to the main analysis: -1.02 g per µg/L (95% CI: −1.71, −0.34). See Appendix C.2 for details.

4.5. DEVELOPMENTAL NEUROCOGNITIVE EFFECTS

The basis for study selection for screening analyses of exposure-response for the developmental neurocognitive effects are described by Hobbie et al. (2020), Section 4.2, and Appendix C.3.1. For developmental neurocognitive effects, the screening-level analyses indicated the Bayesian dose-response meta-analysis approach described in this assessment would not be feasible due to the lack of dichotomous, relative risk studies for this endpoint. Therefore, a dose-response approach similar to that employed for birth weight was used. See U.S. EPA (2025) for access to all dose-response input and output files for developmental neurocognitive effects.

On the basis of literature searches up to September 2024 (see Section 2.1), 63 developmental neurocognitive *high* or *medium* confidence studies were identified and advanced for consideration for dose-response.

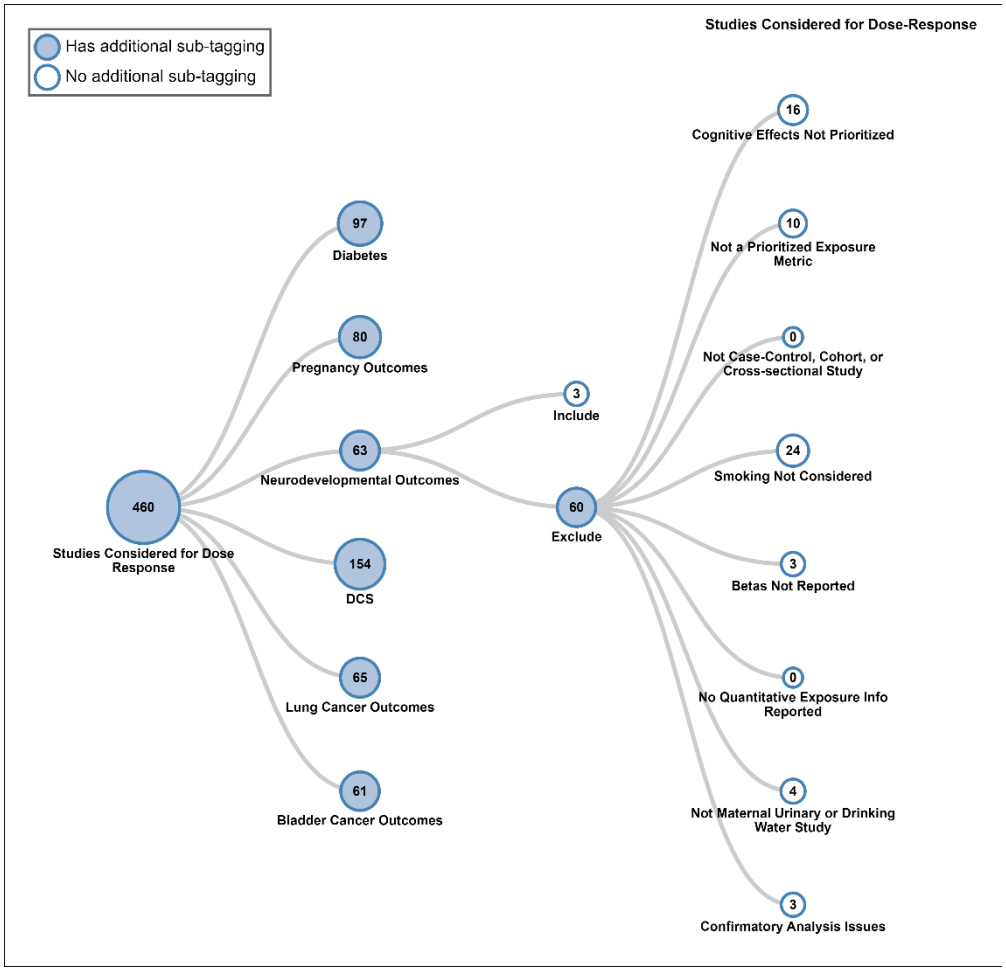


Figure 4-11. Study selection flow for identification of studies for developmental neurocognitive dose-response analyses (see interactive version in HAWC).

For developmental neurocognitive outcomes, one sub-outcome reached an evidence judgment of *moderate*: cognitive deficits. Therefore, studies of cognitive deficits were carried forward for dose-response modeling while other neurodevelopment outcomes were not advanced (i.e., social, behavioral, and emotional effects; motor effects).

As noted in Section 4.3.1, the dose-response study selection for developmental neurocognitive effects now explicitly considers whether a study controlled for maternal smoking during pregnancy and/or secondhand smoke during childhood, given its role as a potential key confounder in the relationship between arsenic and developmental neurocognitive outcomes (Chen et al., 2013a; Anderko et al., 2010).[69] In the conduct of the study-selection process, a study was considered to have addressed smoking if it was reported that mothers in the study did not smoke or were not exposed to secondhand smoke during pregnancy, if a study reported children were not exposed to smoke during childhood, or if smoking was considered in statistical models as a confounder. If a study did not mention smoking or how the authors addressed confounding due to tobacco smoke exposure and smoking rates in the population were anticipated to be non-negligible, the study was excluded from consideration for dose-response. In addition to smoking, other important confounders such as sex, age, socioeconomic status (e.g., education or income) were also considered as part of the study evaluation process (see Section 1.6.2 above and additional details in HAWC: https://hawc.epa.gov/assessment/100500243/). The full list of confounders controlled for in the individual studies are listed in Table C-64.

For other outcomes in this assessment, use of the El-Masri and Kenyon PBPK model (El-Masri and Kenyon, 2008; El-Masri et al., 2018b; El-Masri et al., 2018a) allows for the conversion of urine biomarker data to oral doses. However, there is uncertainty about application of this model to populations of pregnant women or children. Instead, a study by Gilbert-Diamond et al. (2016) that reports the relationship between maternal urinary total As and drinking water concentrations was used to allow for consideration of studies that report maternal urinary concentrations for developmental neurocognitive effects. However, EPA is not aware of an approach to reliably convert childhood urinary total As concentrations into drinking water exposures and thus, these studies are excluded from consideration as shown above in Figure 4-11. Similarly, studies reporting iAs levels in toenails were not considered for developmental neurocognitive effects as the Moon et al. (2013) study that allows the conversion of toenail iAs concentrations into drinking water concentrations was established in adult populations.

Ultimately, three cohort studies were considered for the dose-response of developmental neurocognitive outcomes: a study in Spanish children (Soler-Blasco et al., 2022), a study in U.S. children (Signes-Pastor et al., 2022), and a study in Chinese children (Chen et al., 2023). All of these

[69]Previously, in the external review draft smoking was not a critical criterion considered, and studies that did not control for or address smoking were considered for dose-response Specifically, dose-response for neurocognitive effects was based on the Wasserman et al. (2014) study. This study did not report if mothers smoked during pregnancy or if children lived in a home where smoking occurred. Therefore, while previously considered for dose-response, this study is now excluded based on this criterion.

studies reported beta coefficients for IQ tests (full-scale or subscale) based on maternal urinary total As concentration. The IQ tests reported could all be standardized to the same scale., and they all reported an inverse effect. As three studies is generally considered to be sufficient for conducting a meta-analysis, a point of departure for developmental neurocognitive effects was derived based on a meta-analysis of the three selected studies. See interactive HAWC figure for full list of which studies were excluded under each selection criterion/consideration. The order of appearance of the criteria/consideration in the HAWC figure above reflects the sequence of application (i.e., confirmation of prioritized endpoint was the first screening criteria). Most studies were excluded because they did not adjust for childhood exposure to smoking, did not present analyses of IQ (full-scale or subscale tests), or did not use drinking water or urine as the exposure metric. Several studies passed all but two of the dose-response screening criteria (i.e., they contained information necessary for dose-response modeling) but were ultimately excluded after further consideration of study characteristics. Four studies investigated the effect of iAs on developmental neurocognitive function based on urinary total As measured in the child's urine (Rodríguez-Barranco et al., 2016; Jiang et al., 2022; Desai et al., 2018) or blood (Wasserman et al., 2011). There were methodological issues with three additional studies that precluded their further consideration: Rodrigues et al. (2016) reported that beta coefficients for the association between As concentrations and intellectual test z-scores, Vahter et al. (2020) reported beta coefficients for quantiles of exposure rather than a single continuous beta for the entire population (precluding its inclusion in a meta-analysis with other studies), and Patti et al. (2022) based their analysis on DMA and not total As in maternal urine.

4.5.1. Point of Departure Estimation for Developmental Neurocognitive

All three of the developmental neurocognitive studies that made it through study selection used $\log_2$-transformed maternal urinary tAs concentrations as the exposure metric and thus the reported betas are for decreased IQ points per $\log_2(\mu g/L)$. To derive a POD for developmental neurocognitive effects, a meta-analysis of the three maternal urinary studies was conducted using the study reported beta coefficients to reduce between-study heterogeneity and minimize possible bias from re-expression to the normal scale (i.e., re-expression would only be required for the pooled beta coefficient and not for all three studies used in the meta-analysis). All three studies used different neuropsychological assessments to assess cognitive function at different ages. Soler-Blasco et al. (2022) assessed children at age five using the McCarthy Scale of Children's Ability (MSCA) and reported children's general cognitive index (GCI), standardized to a mean of 100 and standard deviation of 15. Chen et al. (2023) assessed children at age two using the Bayley Scales of Infant Development (BSID), which was translated into Chinese and locally standardized. Chen et al. (2023) reported the children's mental development index (MDI; mean = 100, sd = 15). Lastly, Signes-Pastor et al. (2022) assessed children's cognitive function at multiple time points using multiple instruments. To align as close as possible to the ages assessed in the Soler-Blasco et al. (2022) and Chen et al. (2023) studies, the results for cognitive tests administered at age two and

five in Signes-Pastor et al. (2022) were considered for the meta-analysis. At age two, Signes-Pastor et al. (2022) reported children's MDI assessed using the BSID; at age five, children's full-scale IQ (FSIQ) scores were reported as estimated by the Wechsler Preschool and Primary Scale of Intelligence (WPPSI; mean = 100, sd = 15). All three outcomes (BSID-MDI, MSCA-GCI, WPPSI-FSIQ) can be considered IQ outcomes (White et al., 2022) and therefore are appropriate and amenable to the application of a meta-analysis given all three outcomes are standardized to the same scale (i.e., mean = 100, sd = 15). Both Soler-Blasco et al. (2022) and Chen et al. (2023) reported the results for subsets of the neuropsychological assessments used in those studies, such as multiple subtests of the MSCA (verbal, perceptual performance, quantitative, memory, etc.). However, Signes-Pastor et al. (2022) only reported results for the general IQ scores for the three neuropsychological assessments. Thus, IQ scores from the various neuropsychological assessments consistent with full-scale IQ were used in the dose-response assessment.

For continuous data, the typically preferred definition of the benchmark response (BMR) includes a consideration of what constitutes a minimal level of change in the endpoint that is biologically significant. For IQ, different organizations or authoritative bodies have considered similar decrements to be adverse. For example, ATSDR (2022) used a decrease of 1 IQ point to derive a minimal risk level for methylmercury. ATSDR notes that "[w]hile IQ losses ranging from 1 to 5 points are not significant for most children … these small decrements may represent meaningful intellectual and economic achievement at the population level." Additionally, EPA (2016) used an IQ loss of 2 points as the basis for setting the 2016 Final Rule for the National Ambient Air Quality Standards for Lead based on comments from EPA's Clean Air Scientific Advisory Panel that "… a population loss of 1-2 IQ points is highly significant from a public health perspective."

The hybrid approach was used to define the BMR for developmental neurocognitive effects. For full-scale IQ, adversity can be defined based on the clinical cut-off for mild intellectual disability: IQ below 70 points. The American Psychiatry Association defines mild intellectual disability in school-age children and adults as "… difficulties in learning academic skills involving reading, writing, arithmetic, time, or money, with support needed in one or more areas to meet age-related expectations" (APA, 2013). The clinical definition of mild intellectual disability is a score on a psychometrically valid (White et al., 2022) test of intelligence of approximately two or more standard deviations below the population mean of the test. Given the intellectual tests administered in Signes-Pastor et al. (2022), Soler-Blasco et al. (2022), and Chen et al. (2023) are all standardized to a population mean of 100 and standard deviation of 15, this corresponds to an IQ of 70 representing mild intellectual disability in all of these study populations. Using a standard normal distribution, 2.5% of the population can be expected to fall below this adversity cut-off.

Thus, given the clinical cut-off for adversity (i.e., IQ below 70 points) and the expectation that 2.5% of the population is expected to be below this cut-off, the hybrid approach (U.S. EPA, 2012) was used to define the BMR for this continuous endpoint (see Section 4.4.1 for details on the

hybrid definition of the BMR). For developmental neurocognitive effects, an extra risk of 0.5% was selected, meaning the BMD would be the dose that results in 3% of the responses falling below the 70-point cut-off value:

$$Extra\ Risk(ER) = (P(d) - P(0)) \ / \ (1 - P(0)) \quad (4\text{-}8)$$

$$P(d) = ER(1 - P(0)) + P(0) = 0.005(1 - 0.025) + 0.025 = 0.030 \quad (4\text{-}9)$$

Using the standardized population mean of 100 (standard deviation = 15), EPA calculated the mean response that would be associated with the 3rd percentile of the normal distribution falling below the 70-point cut-off. In this case, the mean IQ score would be 98.24 points, corresponding to a shift in the population mean IQ of approximately 1.75 points. This shift in the population mean IQ is consistent with other dose-response or risk assessment analyses in which shifts of 1 to 2 points are considered adverse (described above).

The meta-analysis for developmental neurocognitive effects resulted in a pooled beta (95% CI) of −1.46 (-3.03, 0.1) IQ points per $\log_2$(µg/L) increase in maternal urinary tAs concentration. However, in order to calculate the BMD and BMDL in units of µg/L, the pooled beta coefficient (and its confidence interval) must first be re-expressed to the normal scale. To do so, the β coefficient is re-expressed in terms of per µg/mL according to Dzierlenga et al. (2020). First, the distribution of exposure for each individual study was estimated by assuming the exposure followed a log-normal distribution. Then, 100 replicates of random samples (sample size was the same as the reported sample size in each study) were simulated from the exposure distributions for each study included in the meta-analysis, and random samples from all studies were pooled for each replicate to get quantiles from the pooled random samples for each replicate. Lastly, the mean quantiles (median and IQR) from the 100 replicates were used to obtain the exposure distribution for all studies using the equations $\mu = ln(q_{50})$ and $\sigma = ln(q_{75}/q_{25})/1.349$ since the joint distribution of the exposures are also log normally distributed. Doing so results in a re-expressed pooled beta (95% CI) of −0.19 (−0.39, 0.01) IQ points per µg/L increase in maternal urinary tAs concentration.[70]

The BMD, in units of µg/L maternal urinary tAs, was calculated by rearranging the equation $y = mx + b$ and solving for x, using 100 points for the b term and −0.19 for the m term. Doing so results in a value of 9.26 µg/L:

$$x = (y - b)/m = (98.24 \text{ IQ points} - 100 \text{ IQ points})/(-0.19\ g(\mu g/L)^{-1}) = 9.26\ \mu g/L \quad (4\text{-}10)$$

To calculate the BMDL, the method is similar, except the lower limit on the β coefficient is used for the m term. A two-sided 95% confidence interval for the β coefficient (−0.39, 0.01 IQ points per µg/L) was estimated from the meta-analysis, meaning that the lower limit of that

[70]A sensitivity analysis in which study-specific $\log_2$-tranformed betas were re-expressed to the normal scale prior to the meta-analysis (instead of performing the meta-analysis on the $\log_2$-transformed betas and re-expressing post-hoc) resulted in almost identical results to the main analysis: a pooled beta of -0.2 IQ points per µg/L (95% CI: -0.38, -0.02). See Appendix C.3.1 for details.

confidence interval corresponds to a 97.5% one-sided lower limit. The BMDL is defined as the 95% lower limit of the BMD (i.e., corresponds to a two-sided 90% confidence interval), so the proper lower limit on the β coefficient needs to be calculated before calculating the BMDL. The standard error of the pooled β coefficient was reported as 0.8, thus the 95% lower confidence limit on the β coefficient is calculated as:

$$95\%\ one\ sided\ LL = \beta - 1.645\big(SE(\beta)\big) = -0.19\ IQ\ points\ (\tfrac{\mu g}{L})^{-1} - 1.645\left(0.38\ IQ\ points\ (\tfrac{\mu g}{L})^{-1}\right) = -0.355\ g(\tfrac{\mu g}{L})^{-1} \quad (4\text{-}11)$$

Using this value for the m term results in a BMDL of 4.96 µg/L. The BMD and BMDL, in units of maternal urinary tAS, were then converted into units of daily iAs intake (in units of µg/kg-day) by first using the Gilbert-Diamond regression equation (as described in Section 4.4.1 and Appendix C.2.1) to convert to units of µg/day, and then dividing by the average body weight for pregnant women (75 kg, U.S. Exposure Factors Handbook, Table 8-29 (U.S. EPA, 2011). This resulted in a BMD of 0.612 µg/kg-day and a BMDL of 0.315 µg/kg-day.

4.6. NONCANCER REFERENCE DOSE (RfD) DERIVATIONS

The noncancer reference dose (RfD) values derived in this section are estimates of the total chronic dose to U.S. populations, including sensitive subpopulations or lifestages, likely to be without appreciable adverse health effects. This assessment derives a single overall RfD to cover all health outcomes across all organs/systems. However, organ/system-specific values are also provided as they can be useful for subsequent cumulative risk assessments that consider the combined effect of multiple exposures acting on a common organ/system or mechanism.

4.6.1. Study and Endpoint Selection

Data sufficient to support RfD derivation for oral inorganic arsenic exposure were available for all health outcomes identified in Section 4.1. Table 4-11 presents a summary of studies, outcomes, and rationales considered for POD derivation.

Table 4-11. Endpoints considered for derivation of points of departure

Outcome	Reference	Exposure duration	POD derived?	Rationale
IHD	Chen et al. (2013c); Moon et al. (2013); James et al. (2015); Wade et al. (2015). Wu et al. (2010b)	Chronic	Yes	Evidence judgment conclusion of evidence demonstrates; multiple high confidence studies met study screening criteria for dose-response meta-analysis as described in iAs Protocol (see Section 5.2.2)
Diabetes	Grau-Perez et al. (2017); James et al. (2013); Coronado-González et al. (2007); Pan et al. (2013b)	Chronic	Yes	Evidence judgment conclusion of evidence demonstrates; multiple high confidence studies met study screening criteria for meta-regression dose-response meta-analysis as described in iAs Protocol (see Section 5.2.2)
Birth weight	Kile et al. (2016); Liu et al. (2018); Rahman et al. (2009); Laine et al. (2015)	Gestational	Yes	Evidence judgment conclusion of evidence indicates (likely); multiple high and medium confidence studies showing effects at relevant exposure levels in US-relevant populations
Neuro-developmental effects	Soler-Blasco et al. (2022); Signes-Pastor et al. (2022); Chen et al. (2023)	Gestational	Yes	Evidence judgment conclusion of evidence indicates (likely); multiple high and medium confidence studies showing effects at relevant exposure levels in US-relevant populations

4.6.2. Estimation of Points of Departure for RfD Derivation

The Bayesian dose-response meta-analysis modeling approach used for diabetes and IHD is discussed in Appendix C.1.1. Briefly, after applying the dose-response meta-analysis approach, the benchmark dose (BMD) for diabetes and IHD health is calculated as (see Appendix C.1.3 for full details):

$$BMD = \sqrt[q]{\frac{\ln(OR)}{\beta}} = \sqrt[q]{\frac{\left(Odds(P_{BMD}) / Odds(P_0)\right)}{\beta}} \quad (4\text{-}12)$$

Where P_{BMD} and P_0 are the probabilities associated with 5% and 0% extra risk, respectively, and extra risk is defined as:

$$Extra\ risk = \frac{P_{BMD} - P_0}{1 - P_0} \quad (4\text{-}13)$$

The β and q parameters are the mean pooled logistic slope and power parameters estimated during the Bayesian hierarchical dose-response meta-analysis. BMDs were obtained for diabetes and IHD by solving the equations in Appendix C.1.3 for each ordered sampled pair of β and

q from the full posterior distribution and taking the median value. The BMDL for each endpoint was set equal to the 5th percentile of those calculated values.

When calculating a BMD or BMDL, the particular benchmark dose response (BMR) level must be selected a priori in order to perform benchmark dose modeling. Two important considerations in the selection of a BMR level are the severity of the response and whether the resultant BMD would be within the range of the data, preferably near the low end of the observable responses. The effects under consideration, clinically diagnosed type 2 diabetes and IHD, both have a high (40%) lifetime probability of occurrence within the U.S. population (see Section 4.3.4). Diabetes, while a chronic disease, is not considered a frank effect and does not warrant a lower BMR than 5% on the basis of severity. The selection of the BMR for IHD is more complicated given that studies reporting IHD are sometimes incidence studies with no fatal cases of IHD or sometimes include both incident and fatal cases. In the case of the five studies included in the IHD Bayesian dose-response meta-analysis, two studies (Wu et al., 2010b; Wade et al., 2015) were incidence-only studies. EPA does not consider incident cases of IHD as frank effects and thus would select a BMR of 5% extra risks for studies of exclusively incident cases. The remaining three IHD studies (Moon et al., 2013; James et al., 2015; Chen et al., 2013c) included both incident and fatal cases of IHD. The Moon et al. (2013) study provided the incidence numbers for the fatal + incidence and fatal only analyses, the number of incidence cases was calculated and shown to predominate total incidence at low doses (comprising approximately two-thirds of total cases). Overall, the Moon et al. (2013) study reported a roughly 60% incident cases and 40% fatal cases breakdown. Although incidence-only numbers cannot be calculated for the Chen et al. (2013c) or James et al. (2015) studies, it is reasonable to assume this same pattern holds. Therefore, given the mix of incidence-only studies and incidence + fatal studies in the dose-response meta-analysis and BMD derivation, EPA applied a BMR of 5% extra risk for incident cases of IHD and a 1% BMR to fatal cases of IHD, weighted by sample size (see Appendix C.1.3 for full details).

For fetal, newborn, and infant health outcomes, the modeling approach taken was to apply the hybrid benchmark response approach using the pooled beta coefficient for the association of iAs exposure to decreased fetal weight calculated in a three-study meta-analysis (see Section 4.4). A BMR of 5% was selected for this endpoint because the developmental effects were observed during a potentially sensitive lifestage and because a 5% change in markers of growth/development in gestational studies (e.g., fetal weight) has been considered a minimally biologically significant response level.

For developmental neurocognitive effects, the modeling approach taken was to apply the hybrid benchmark response approach using the pooled beta coefficient for the association of iAs exposure to decreased childhood IQ scores calculated in a three-study meta-analysis (see Section 4.5). A BMR of 0.5% was selected for this endpoint given that it corresponds to a decrease in population mean IQ score of approximately 1.75 points and a shift in population IQ of this magnitude has been determined to be relevant to public health (ATSDR, 2022; 2016).

Table 4-12. Points of departure (PODs) considered for use in deriving candidate toxicity values for iAs

Health outcome	Study	Basis for point of departure	Point of departure (µg/kg-d)
Diabetes	Dose-response meta-analysis of four studies	$BMDL_{05}$[a]	0.174
IHD	Dose-response meta-analysis of five studies	$BMDL_{01,05}$[a]	0.171
Birth weight	Meta-analysis of three studies	$BMDL_{05}$[b]	1.4
	Kile et al. (2016)	$BMDL_{05}$[c]	0.237
IQ score	Meta-analysis of three studies	$BMDL_{005}$[d]	0.315

[a]BMDL calculated as described in Appendix C.1.3.

[b]A $BMDL_{05}$ of 48 µg iAs/L maternal urinary tAs was first estimated using the hybrid approach as described in Section 4.4 of the assessment, with the BMDL representing the one-sided 95% lower confidence limit on the µg tAs/L exposure that results in an extra risk of 5% of the exposed population having a birth weight below the defined adversity threshold of 2,500 g. This was then converted to 1.4 µg/kg-day total dose using the approach described in Appendix C.2.1.

[c]A $BMDL_{05}$ of 18.7 µg iAs/L maternal urinary tAs was first estimated using the hybrid approach as described in Section 4.4 of the assessment, with the BMDL representing the one-sided 95% lower confidence limit on the µg tAs/L exposure that results in an extra risk of 5% of the exposed population having a birth weight below the defined adversity threshold of 2,500 g. This was then converted to 0.237 µg/kg-day total dose using the approach described in Appendix C.2.1.

[d]A $BMDL_{05}$ of 4.96 µg iAs/L maternal urinary tAs was first estimated using the hybrid approach as described in Section 4.5 of the assessment, with the BMDL representing the one-sided 95% lower confidence limit on the µg tAs/L exposure that results in an extra risk of 0.5% of the exposed population having an IQ score below the defined adversity threshold of 70 points. This was then converted to 0.315 µg/kg-day total dose using the approach described in Appendix C.3.1).

4.6.3. Derivation of Candidate Toxicity Values

Under EPA's *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b) and *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), five areas of uncertainty and variability were considered in deriving the candidate toxicity values for iAs. Table 4-13 presents an explanation of these five areas of uncertainty and variability and the values assigned to each as designated uncertainty factors (UFs) for application to the candidate toxicity values.

Table 4-13. Uncertainty factors for the development of the candidate toxicity values for inorganic Arsenic (iAs)

UF	Value	Justification
UF_A	1	A UF_A of 1 is applied to account for uncertainty in characterizing the toxicokinetic and toxicodynamic differences between experimental animals and humans following oral iAs exposure given that epidemiological studies are exclusively used for the derivation of the RfD.
UF_H	3	A UF_H of 3 is applied to account for potential interindividual differences in pharmacokinetics and pharmacodynamics relating to iAs exposure in humans. A higher UF_H is not necessary for IHD, diabetes, fetal, newborn, and infant health outcomes, or developmental neurocognitive PODs resulting from dose-response meta-analyses. These multistudy meta-analyses investigated a heterogeneous mix of multiple study populations, each of which included and adjusted for many sensitive subpopulations and confounders, including smokers, sex, nutritional status, lifestage, genetic variability, and methylation capacity. Results of the extensive leave-one-out sensitivity analyses showed that when studies are iteratively left out of the Bayesian dose-response meta-analyses of IHD or diabetes, the exclusion of a single study does not reduce the estimated pooled logistic slope by more than 63%: excluding the James et al. 2015) IHD study reduces the pooled slope by 61% and excluding the Grau-Perez et al. (2017) diabetes study reduces the pooled slope by 23%. Stated another way, when a single study (possibly reflecting subpopulation sensitivity) is included in the dose-response meta-analysis, the pooled slope never increases by more than ~2.5-fold. This suggests that application of a full 10-fold uncertainty factor to account for interindividual differences is not warranted and a 3-fold UF was applied instead. A higher UF_H was not deemed necessary for the fetal, newborn, and infant POD derived from the Kile et al. (2016) study. The Bangladeshi population that formed the basis of this birth weight POD is known to have a major public health problem with low birth weight, with a notable difference between its 21% background prevalence and the 8.3% U.S. background prevalence (see discussion in Section 4.4). Further, the effect observed in the Kile et al. (2016) study was much stronger than the pooled effect derived by that meta-analysis. EPA considers this to be support that the Kile et al. (2016) study represents a sensitive subpopulation with respective to susceptibility and that a full $UF_H = 10$ is not warranted for this study. Conversely, even though this study population does represent a sensitive subpopulation, it is not likely the most sensitive subpopulation and reducing the UF_H to 1 is also not warranted. Overall, a 3-fold UF is warranted to account for potential interindividual differences in pharmacokinetics and toxicodynamics within the sensitive subpopulations included in the meta-analysis and single study analysis and the fact that a limited set of sensitive populations have been studied and may not represent the total spectrum of sensitive groups. However, when considering population variability, specifically within the context of the entire U.S. population, use of data from these sensitive groups of individuals largely predisposed to developing such effects (as compared with U.S. individuals) does not warrant a higher than 3-fold UF.
UF_S	1	A UF_S of 1 is applied to endpoints observed in the epidemiological studies as most of the studies in the dose-response meta-analysis investigated chronic exposures. Many study populations in the epidemiological studies were assumed to be exposed to iAs for a lifetime and of the studies that explicitly report the duration of exposure, the average was approximately 30 yr. A UF_S of 1 is also applied to endpoints observed in gestational epidemiology studies as the developmental period is recognized as a susceptible lifestage where exposure during certain time windows (e.g., pregnancy and gestation) is more relevant to the induction of developmental effects than lifetime exposure.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation when the POD is determined by modeling or identification of NOAEL.

UF	Value	Justification
UF_D	1	A UF_D of 1 is applied given the database of iAs epidemiologic studies is expansive. Identification of studies to include in the dose-response analyses was initially based on a screening-level analysis of 12 endpoints consisting of >200 studies or data sets. From this screening-level analysis, endpoints with the largest databases and percentage of studies with results within 10-fold of the U.S. background iAs exposure (i.e., strongest dose-response relationships) were selected for the Bayesian dose-response meta-analyses. Therefore, an endpoint selection process was used to preferentially advance endpoints with large, complete databases and evidence indicating strong associations of iAs exposure and disease at lower doses. Additionally, the fetal, newborn, and infant health outcome of birth weight and developmental neurocognitive outcome were advanced for additional dose-response analysis and thus, concern over developmental endpoints deriving lower PODs is mitigated as these PODs are considered alongside the PODs derived via dose-response meta-analysis.
UF_C	See Table 4-14	Composite uncertainty factor = $UF_A \times UF_H \times UF_S \times UF_L \times UF_D$.

Table 4-14 lists the candidate toxicity values for iAs as determined after the application of UFs. As described in EPA's *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b), the intraspecies uncertainty factor (UF_H) is applied to account for "variations in susceptibility within the human population (i.e., interhuman variability) and the possibility (given a lack of relevant data) that the database available is not representative of the dose/exposure-response relationship in the subgroups of the human population that are most sensitive to the health hazards of the chemical being assessed."

Table 4-14. Candidate toxicity values for inorganic arsenic (iAs)

Endpoint	POD (µg/kg-d)	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate toxicity value (µg/kg-d)
Diabetes	0.174	1	3	1	1	1	3	0.058
IHD	0.171	1	3	1	1	1	3	0.057
Birth weight – meta-analysis	1.4	1	3	1	1	1	3	0.47
Birth weight – (Kile et al., 2016)	0.237	1	3	1	1	1	3	0.079
IQ score	0.315	1	3	1	1	1	3	0.105

4.6.4. Selection of Lifetime RfD(s)

From among the candidate toxicity values presented in Table 4-14, organ/system-specific RfD (osRfDs) are selected for IHD, diabetes, fetal, newborn, and infant health, and developmental neurocognitive outcomes. Among the two osRfDs for birth weight, the osRfD derived from the Kile et al. (2016) study was selected. Although meta-analyses were preferred, the osRfD derived from the Kile et al. (2016) study was 6-fold lower than the osRfD derived from the three-study meta-analysis. Therefore, the Kile et al. (2016) osRfD was selected in order to ensure health-protectiveness for this endpoint.

The confidence decisions about the study, evidence base, POD quantification, and overall RfD for these organ/system-specific values are fully described in Table 4-15, along with the rationales for selecting those confidence levels. In deciding overall confidence, confidence in the evidence base is prioritized over the other confidence decisions. The overall confidence in the organ/system-specific RfDs for diabetes and IHD is *high,* and the overall confidence in the organ-specific RfD for fetal, newborn, and infant health outcomes is *medium-low*.

Table 4-15. Organ/system-specific oral RfDs and confidence for iAs

Confidence categories	Designation	Discussion
Diabetes RfD = 0.058 µg/kg-d		
Confidence in studies[a] used to derive organ/system-specific RfD	High	Confidence in the studies used in the hierarchical Bayesian dose-response meta-analysis of diabetes is *high* given the analysis is based on the modeling of multiple studies together and these studies were all judged to have study confidence ratings of *high* or *medium*.
Confidence in evidence base supporting this hazard	High	Confidence in the evidence base for diabetes effects is *high* as the hazard conclusion for this endpoint was that "currently available evidence demonstrates that inorganic arsenic causes diabetes in humans under relevant exposure circumstances" (see Section 3.2.2).
Confidence in quantification of the POD_{HED}	High	Confidence in the quantification of the POD and organ-specific RfD is *high* given the point of departure was based on the hierarchical Bayesian dose-response meta-analysis of multiple high and medium confidence studies within the range of the observed data.
Overall confidence in organ/system-specific RfD	High	The overall confidence in the RfD is *high* given that the confidence in individual components of the overall confidence determination is also *high*.
DCS RfD = 0.057 µg/kg-d, based on IHD		
Confidence in studies[a] used to derive organ/system-specific RfD	High	Confidence in the studies used in the hierarchical Bayesian dose-response meta-analysis of IHD is *high* given the analysis is based on the modeling of multiple studies together and these studies were all judged to have a study confidence rating of high or *medium*.
Confidence in evidence base supporting this hazard	High	Confidence in the evidence base for IHD effects is *high* as the hazard conclusion for this endpoint was that "there is robust evidence from a large set of high and medium confidence epidemiologic studies of varied design that demonstrate iAs exposure can cause cardiovascular effects in humans under relevant exposure circumstances" (see Section 3.2.1).

Confidence categories	Designation	Discussion
Confidence in quantification of the POD_{HED}	Medium-high	Confidence in the quantification of the POD and organ-specific RfD is *medium-high* given that there is some uncertainty pertaining to the selection of the benchmark response for this endpoint. However, the point of departure was based on the hierarchical Bayesian dose-response meta-analysis of multiple high and medium confidence studies within the range of the observed data, ultimately supporting the determination of *medium-high* confidence.
Overall confidence in organ/system-specific RfD	Medium-high	The overall confidence in the RfD is *medium-high* and is primarily driven by medium-high confidence in the quantification of the POD.
Birth weight RfD = 0.079 µg/kg-d		
Confidence in studies[a] used to derive organ/system-specific RfD	High	Confidence in the study used in the dose-response analysis for birth weight is *high* based on low risk of bias, a study design that accounted for potential confounders, exposure characterization, and other characteristics that allowed for adequate study sensitivity to detect associations.
Confidence in evidence base supporting this hazard	Medium	Confidence in the evidence base for birth weight (fetal, newborn, and infant health outcomes) is *medium* as the hazard conclusion for this endpoint was that "the currently available epidemiologic evidence indicates that iAs likely causes fetal, newborn, and infant health outcomes in humans given sufficient exposure conditions" (see Section 3.2.3).
Confidence in quantification of the POD_{HED}	Medium-low	Confidence in the quantification of the POD and organ/system-specific RfD is *medium-low*. Lack of information on the potential differences in pharmacokinetics and toxicodynamics relating to iAs exposure in U.S. populations, and the uncertainty associated with extrapolating U.S. risk from a study of a single population with a substantially higher sensitivity for this specific outcome, decreases the confidence. That the POD was based on a BMD hybrid approach within the range of the observed data increases confidence.
Overall confidence in organ/system-specific RfD	Medium-low	The overall confidence in the organ/system-specific RfD is *medium-low* and primarily driven by *medium-low* confidence in the quantification of the POD.
IQ score RfD = 0.105 µg/kg-d		
Confidence in studies[a] used to derive organ/system-specific RfD	High	Confidence in the studies used in the meta-analysis of birth is *high* given the analysis is based on the modeling of multiple studies together and these studies were all judged to have a study confidence rating of *high* or *medium*.
Confidence in evidence base supporting this hazard	Medium	Confidence in the evidence base for developmental neurocognitive effects (IQ score) is *medium* as the hazard conclusion for this endpoint was that "the currently available evidence indicates that iAs likely causes neurodevelopmental effects in humans given sufficient exposure conditions" (see Section 3.2.4).

Confidence categories	Designation	Discussion
Confidence in quantification of the POD_{HED}	Medium	Confidence in the quantification of the POD and organ/system-specific RfD is *medium* given that the POD was based on a BMD hybrid approach within the range of the observed data increases confidence and dosimetric adjustment was based on the empirical relationship between drinking water exposure and maternal urinary total As concentrations.
Overall confidence in organ/system-specific RfD	Medium	The overall confidence in the organ/system-specific RfD is *medium* and primarily driven by *medium* confidence in the evidence base supporting this hazard and the quantification of the POD.

[a]All study evaluation details can be found on HAWC.

Table 4-16 summarizes organ/system-specific RfDs for iAs selected in the previous section.

Table 4-16. Organ/system-specific oral RfDs for iAs

System	Basis	POD (µg/kg-d)	UF_C	RfD iAs (µg/kg-d)	Confidence
Diabetes	Type 2 diabetes mellitus	0.174	3	0.058	High
Cardiovascular	IHD	0.171	3	0.057	Medium-high
Fetal, newborn, and infant health outcomes	Birth weight	0.237	3	0.079	Medium-low
Developmental neurocognitive	IQ score	0.315	3	0.105	Medium

From the identified human health effects of iAs and the derived organ/system-specific RfDs for cardiovascular effects, diabetes, fetal, newborn, and infant health outcomes, and developmental neurocognitive effects (see Table 4-16), an RfD of 0.06 µg/kg-day, based on increased incidence of diabetes and IHD in humans, was selected as the overall RfD.[71] The 0.06 µg/kg-day RfD represents an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure (above zero dose) for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable increased risk of diabetes or IHD (over the estimated risk at zero dose) during a lifetime. As described in Table 4-15 confidence in the osRfDs is *high* for diabetes and *medium-high* for IHD (acknowledging the uncertainty in selecting the BMR for this endpoint). Accordingly, the overall confidence in the final RfD is *medium-high*. While the IHD organ/system-specific RfD is based on the lowest POD_{HED} using a dose-response

[71]As a reminder, the estimated background dose of 0.0365 µg/kg-day is assumed to be associated with the estimated background risk of IHD.

meta-analysis approach that included *high* and *medium* confidence studies (0.171 µg/kg-day, compared with 0.174 µg/kg-day for diabetes), rounding the resulting organ-specific RfDs to one significant digit results in identical values (i.e., 0.06 µg/kg-day). The final RfD is expected to be protective against all noncancer adverse health effects associated with iAs and across all life stages. The decision to base the final RfD on both IHD and diabetes was based on all available organ-specific RfDs in addition to overall confidence and composite uncertainty for those RfDs.

4.6.5. Previous IRIS Assessment: Reference Value

The previous non-cancer IRIS assessment for inorganic arsenic was posted to the IRIS database in 1991. An oral reference dose (RfD) of 3×10^{-4} mg/kg-day (0.3 µg/kg-day) was developed based on a NOAEL for increased hyperpigmentation, keratosis, and possible vascular complications in a human population in an endemic area of chronic arsenic exposure in Taiwan (Tseng et al., 1968; Tseng, 1977). A UF_C of 3 was applied to the NOAEL identified in these studies to account for both lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL accounts for all sensitive individuals. This RfD was interpreted with **medium** confidence, based on *medium* confidence in the principal studies and *medium* confidence in the database.

4.7. CANCER TOXICITY VALUES

As stated in Sections 4.3.5 (bladder cancer) and 4.3.6 (lung cancer), cancer slope factors were derived as the slope of the linear trendline for the upper confidence limit (i.e., 95% upper bound on risk; UCL) on the extra risk associated with doses above background. Although EPA's modeling approach in this assessment does not assume linearity in response, linear trendline slopes for bladder cancer (1.76×10^{-2} per µg/kg-day) and lung cancer (2.13×10^{-2} per µg/kg-day) were provided as the endpoint-specific CSFs below 0.2 µg/kg-day. This dose level (0.2 µg/kg-day) was selected as the upper dose limit to calculate the CSF because Mendez et al. (2017) reports that the 95th percent upper bound on drinking water concentrations in the United States is 15.4 µg/L, translating to approximately 0.19 µg/kg-day iAs daily intake using a 0.011 L/kg-day water consumption rate and accounting for 0.02 µg/kg-day daily iAs exposure via the diet. Therefore, the provided linear CSFs below this daily dose covers the majority of drinking water exposure scenarios in the United States. The CSFs only provide approximations of the upper-bound lifetime extra risks explicitly calculated using the lifetable approach and using the CSF can result in overestimates of the lifetable risks approximately 20% (bladder cancer) or 15% (lung cancer) at very low doses (i.e., 0.005–0.01 µg/kg-day). Given the nonlinearity in upper-bound lifetime extra risks, linear trendlines beyond 0.2 µg/kg-day are associated with increasingly imprecise estimates, and EPA recommends that the polynomial trendlines provided for bladder cancer and lung cancer be used for daily intakes of up to 1.0 µg/kg-day (see Sections 4.3.5 and 4.3.6). Tables C-31 (bladder cancer) and C-41 (lung cancer) also provide lifetable-calculated risks at daily intakes of 0 µg/kg-day

to 1.5 µg/kg-day, at increments of 0.005 µg/kg-day (i.e., mean and 95% upper-bound lifetime extra risk values are reported for 300 daily intake values). Users that need to generate exact mean or upper-bound lifetime extra risk values at daily intakes other than those reported in Tables C-31 or C-41 can use the Bayesian logistic-power modeling results and lifetable R codes (U.S. EPA, 2025). See the structured workflow, outline, and variable dictionary (U.S. EPA, 2024b) for documentation of modeling files.

A combined cancer slope factor, representing the risk of developing either bladder cancer or lung cancer, or bladder and lung cancer, was derived using the method outlined below and described in the Toxicological Review of Chloroprene (U.S. EPA, 2010). Assuming the cancer slope factors are normally distributed, the combined cancer slope factor is calculated as:

$$Combined\ CSF = \sum MLE\ slope\ factors + 1.645 * composite\ SD \quad (4\text{-}14)$$

The MLE slope factors are the slopes of the linear trendlines fit to the mean lifetime extra risks in Figures 4-6 (bladder cancer) and 4-7 (lung cancer). The composite SD is calculated as:

$$\sqrt{\sum variances} = \sqrt{\sum \left(\frac{upper\ bound - MLE}{1.645}\right)^2} \quad (4\text{-}15)$$

Therefore, the combined cancer slope factor is calculated as:

$$Combined\ CSF = (0.0062 + 0.0078) + \left(\sqrt{\left(\frac{0.0176-0.0062}{1.645}\right)^2 + \left(\frac{0.0213-0.0078}{1.645}\right)^2} \times 1.645\right) =$$

$$3.17 \times 10^{-2} \left(\frac{\mu g}{kg} - day\right)^{-1}$$

A combined cancer polynomial trendline was derived using the methods below in order to estimate combined cancer risks above 0.2 µg/kg-day. This approach should be used for exposures greater than 0.2 µg/kg-day because that is the maximum dose for which the linear iAs cancer slope factor (CSF) is considered reliable. To estimate combined cancer risks below 0.2 µg/kg-day, the linear CSF should be used.

First, the estimated probabilities of developing either bladder cancer or lung cancer at zero exposure was determined using the lifetable for each tumor. These probabilities were $P_{bladder}(0) = 0.01897$ and $P_{lung}(0) = 0.0571$.

The probability of developing one or both of the tumors at zero exposure is given as:

$$P_{bladder,lung}(0) = 1 - \left[\left(1 - P_{bladder}(0)\right) * \left(1 - P_{lung}(0)\right)\right] \quad (4\text{-}16)$$

Then, $ER_{bladder}(d)$ and $ER_{lung}(d)$ (where d equals the dose for which the risk calculation is made) were set as the polynomial trendlines for the 95th upper bound on risk for the individual tumor types as reported in Table 4-10:

$$ER_{bladder}(d) = 0.0184x^2 + 0.0137x$$

and

$$ER_{lung}(d) = 0.0074x^2 + 0.0206x$$

The probability of each of the tumor types is then given by:

$$P_{bladder}(d) = \left[(0.0184x^2 + 0.0137x) * \left(1 - P_{bladder}(0)\right)\right] + P_{bladder}(0) \quad (4\text{-}17)$$

and

$$P_{lung}(d) = \left[(0.0074x^2 + 0.0206x) * \left(1 - P_{lung}(0)\right)\right] + P_{bladder}(0) \quad (4\text{-}18)$$

The probability of developing one or both of the tumors is given by:

$$P_{bladder,lung}(d) = 1 - \left[\left(1 - P_{bladder}(d)\right) * \left(1 - P_{lung}(d)\right)\right] \quad (4\text{-}19)$$

Then, the lifetime extra risk of developing one or both tumors is given by:

$$ER_{bladder,lung}(d) = \frac{P_{bladder,lung}(d) - P_{bladder,lung}(0)}{1 - P_{bladder,lung}(0)} \quad (4\text{-}20)$$

Calculating the lifetime extra risk of developing one or both tumors across a range of doses results in a polynomial trendline approximately given by $combined\ risk = 0.0243x^2 + 0.035x - 0.0001$, see Figure 4-12 below. Note that this trendline is only valid for estimating combined cancer risks above 0.2 µg/kg-day. To estimate combined cancer risks below 0.2 µg/kg-day, the linear CSF should be used instead.

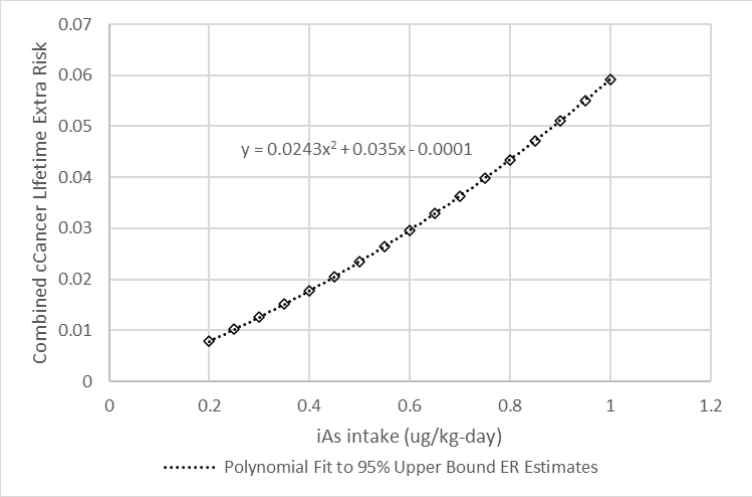


Figure 4-12. Combined cancer lifetime extra risks versus µg/kg-day iAs doses for doses up to 1.0 µg/kg-day

Thus, the lifetime extra risk of developing one or both tumors for a given dose can be approximated for any dose of interest using the equation of the trendline. For example, the lifetime extra risk of developing one or both tumors at a daily intake of 0.25 µg/kg-day would be:

$$ER_{bladder,lung}(0.25) = (0.0243 * (0.25)^2) + (0.035 * 0.025) - 0.0001 = 0.0102$$

Conversely, for a given lifetime risk of developing one or both tumors, the quadratic formula can be used to solve for the daily intake value. For example, for a lifetime extra risk of 0.015, application of the quadratic formula returns two roots: 0.35 µg/kg-day and -1.78 µg/kg-day. Because a negative daily dose is not possible, the daily intake of iAs associated with a lifetime extra risk of development one or both tumors would be 0.35 µg/kg-day. This can be visually confirmed by examining Figure 4-12.

4.7.1. Previous IRIS Assessment: Cancer Slope Factor

The previous cancer IRIS assessment for inorganic arsenic was posted to the IRIS database in 1995. EPA's 1995 IRIS assessment classified inorganic arsenic as "Group A – human carcinogen" under the 1986 guidelines (U.S. EPA, 1986). This was based on sufficient evidence from human data for increased lung cancer mortality in multiple populations exposed via inhalation and increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and increased skin cancer in populations consuming drinking water contaminated with arsenic. A cancer slope factor of 1.5 per mg/kg-day was developed based on skin cancer observed in the same Taiwanese population the RfD was based on (Tseng et al., 1968; Tseng, 1977). The multistage model, with time as a variable, was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic.

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***Errata* for the document titled, IRIS Toxicological Review of Inorganic Arsenic (Final Report) (CASRN 7440-38-2), EPA/635/R-25/005**

Page	
XIV	Clarified RfD derivation regarding developmental neurocognitive effects (January 2025).
XV-XVI	Clarified candidate RfD for fetal, newborn, and infant health outcomes, overall RfD confidence, and Table ES-1 footnote *a* (January 2025).
XVIII	Clarified location of lifetime extra risk tables in the appendices (January 2025).